Dermatological preparations for the tropics

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To the reader of this book

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tries. They are not characterised as such. The use of such names does not n
preference for a specific brand product.

Medicine and pharmacy are scientific fields in which changes can be very
great care to ensure that the opinions, as well as the practical information, i
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Preface

This formulary is a publication of the Scienceshop for Medicine (Wetenschapswinkel voor Geneesmiddelen) of the University of Groningen in the Netherlands. The local production of medicines for use in tropical Trird World countries is one of the fields of interest of the Scienceshop, which resulted in various publications during the past few years. The work leading to this book was financially supported by the Office for International Co-operation of the University of Groningen and by the Stichting Studiefonds Dermatologie.

Skin diseases are one of the most common reasons for seeking medical advice in the Third World. Although skin diseases are in general not life threatening, they may cause much discomfort and often have serious social implications. The potential demand for skin preparations is enormous in a vast area of the world with minimal financial possibilities. Fortunately, most skin diseases can be treated with cheap and simple preparations. However, little scientific work has been done to determine which of a vast number of cheap and simple preparations can be considered an optimal choice for use in tropical conditions. This formulary is an attempt to make such an optimal choice, based on the available scientific information supplemented by own investigations. Studies to compare the cost effectiveness of the chosen preparations with more expensive preparations in use in the rich Weatern countries are in general lacking, but very much needed. We hope dermatological departments with possibilities to conduct such studies will be stimulated by reading this book to do so.

The book aims to meet basic dermatological needs on primary and secondary health care level in poor tropical Trird World countries with emphasis on local production. It is divided into two parts. The first is a practical manual for the preparation and dispensing of dermatologicals being the actual formulary, the second part deals with the backgrounds for the selection, formulation and stability of dermatologicals.

The first part of the book is written from a farmaceutical point of view. It provides an overview of methods and standards for the local production of dermatologicals and quite a large number of preparations. Neither intend to be a blue-print for setting up local production, but provide a background for designing local production which fits ones own specific needs and financial possibilities.

In more detail the chapters 1, 2 and 3 can be used for setting up local production, but also for the training of personnel. Chapter 1 deals with **general notes** on amounts to prepare, packaging, labelling, storage, weights and measures; chapter 2 with **basic standards** of good manufacturing practices for local producing facilities in tropical countries, dealing with personnel, hygiene, premises, equipment and manufacturing procedures, and chapter 3 with **basic methods** like weighing, measurement of liquids, making up to volume or weight, seiving, mixing and heating.

Chapter 4 deals with the **indications for included preparations** and chapter 5 presents the **preparations**. One will notice that very rare skin diseases are not included in the book. The reason therefore is that local production, especially on primary health care level in poor countries, can only be set up from a general point of view. For primary health care with very limited financial resources it is suggested to restrict the number of preparations to about six. Such a limited formulary may for example contain calamine lotion as a soothing and antipruritic preparation, one scabicide, one anti-infective drug like gentianviolet solution, one emollient like emulsifying ointment, and one preparation with an effect on chronic itching skin diseases like hydrocortisone ointment or tar paste. For the secondary health care level more preparations can be chosen, according to the local needs. The preparations are set up in monographs for small scale production, in amounts of 100 g or 100 ml. For stock preparations quantities of 1 kg or 1 litre, or even larger batches are usually prepared. To enable the development of master formulas for stock preparations, we have included 16 master formulas to prepare quantities of 1 kg or 1 litre. The master formulas are printed on loose sheets and are included in the cover at the back of this book.

Chapter 6 lists the **raw materials** used in the preparations. The monographs also provide

information on the storage of the raw materials. Chapter 7 gives a **vocabulary** of the pharmaceutical terms used in the formulary and chapter 8 a **list of synonyms** of preparations and raw materials.

The second part of the book is written from a medical and pharmaceutical point of view. This part may be particular useful in the selection of active substances and pharmaceutical forms for the local production. Also it can be used as an introduction in dermatological therapy. Chapter 9, the **introduction of dermatological preparations for the tropics**, gives backgrounds on the essential drugs concept, basic needs for tropical dermatology and our criteria for selecting preparations for the formulary. In chapter 10, **dermatological therapy**, drugs are discussed according to their therapeutic or pharmacological category. The next therapeutic groups are dealt with: anti-infective drugs used in bacterial, mycotic and parasitic infections, burn wounds and the treatment of ulcers in leprosy, corticosteroids, astringents, keratoplastics and keratolytic agents, moisturizers and special attention to the management of dry skin in leprosy, antimitotics, antipruritics, "indifferent" vehicles and sunscreen agents. Chapter 11, **dermatological vehicles for tropical use**, discusses ointments, pastes, creams and shake solutions. Different formulations are discussed in relation to the tropical climate conditions in which they are to be produced and used. In chapter 12, **stability of drugs**, an introduction to chemical, physical and microbiological stability is given, also in relation to packaging. The chemical stability of unstable therapeutic groups is discussed. Two tables summarize the data on chemical and physical stability.

A **general index** for both parts of the book is included as chapter 13. It lists keywords, preparation- and substance names. Difficult words and technical terms are not avoided in this book. Those, used in the first part, are explained in the vocabulary, chapter 7. Difficult words in the second part of the book are not explained explicitly. In part one no literature references are given. The information given relies on the second part of the book and literature references mentioned there. In the second part each paragraph includes literature references. Therefore, the general index and list of synonyms might be useful to find relevant sources of information. Handbooks used throughout a chapter are listed at the end of the chapters 10, 11 and 12.

The book can be used in many ways. It can be used as a manual for preparation and dispensing of dermatologicals in tropical Thrid World countries. It can also be used as a learning book. And, last but certainly not least, it can be used together by doctors, pharmacists, nurses and other health care workers to develop local drug policies and formularies for dermatologicals.

Part I:

A formulary of dermatological preparations

1 General notes

1 amounts to be prepared

The formula for preparations are written for a standard quantity of 100 grams or 100 ml. Other quantities may of course be prepared. Proceed as follows:

1. Determine the multiplication factor. This is the amount desired divided by the standard amount.
2. Multiply the amount of each ingredient by this multiplication factor.

An example: You want to prepare 500 grams of emulsifying ointment. The multiplication factor is 500/100 = 5. The amounts of ingredients needed are: lanette wax 5 x 30 g = 150 g, liquid paraffin 5 x 25 g = 125 g, petrolatum 5 x 45 g = 225 g.

All quantities mentioned under preparation should also be multiplied by the multiplication factor. The evaporation losses that occur when water is boiled are relatively smaller if larger quantities of water are boiled. The excess water that has to be boiled and cooled can therefore be relatively smaller in large scale production.

The preparation methods given are adjusted to simple small scale production of drugs. In general, this means manual production without machines. Large amounts can not always be prepared manually, machines may be needed. Some of the preparation methods may have to be adapted to preparation with machines, for example because the mixing efficiency may be different. As a general rule, quantities up to 1 kilogram or 1 litre may be prepared manually. Sixteen preparations have already been adapted to prepare amounts of 1 kg or 1 litre. These model master formulas are included in the cover at the back of this book.

2 quality assurance

The quality assurance of a preparation cannot solely be based on control of the end product. As quality control frequently involves a destructive examination of the sample, it is practically impossible to examine every product of a batch, simply because this would not leave anything to dispense. The total quality of a drug is as much determined by the pharmaceutical design and the manufacturing process as by end product control. Mistakes and poor quality should be avoided. This is a much better way than allowing mistakes and trying to find faulty products at the end control.

Good manufacturing practices are even more important when the means for end product control are lacking, as may be the case in many Third World countries. Therefore a set of basic standards for good manufacturing practice for local production units in tropical countries is included in this formulary. These standards are adjusted to the Third World situation and concern personnel, hygiene, buildings, equipment and preparation procedures.

The importance of people in this aspect cannot be over-emphasized. Poor quality of drugs is most often due to human error or even carelessness.

Basic standards for good manufacturing practice include rules for administration. This is a very important aspect. For every preparation for the stock or directly dispensing to the patient, an administration formula should be used. As an example a model master formula, based on the preparation monograph of calamine lotion, is included (figure 1.1).

Master formulas should be developed for each preparation that is to be produced. They should be fairly detailed, and should therefore always be written for the specific, local situation, considering the usual batch size, available apparatus etc. For 16 preparations included in this formulary model master formulas have been developed. They are set up to prepare stock

batches of 1 kg or 1 litre. The preparation methods are the same as for the small scale production of 100 g or 100 ml. Included are models for labels for stock storage, as well as models for labels for the patient. The master formulas are included as loose sheets in the cover at the back of this book.

3 amounts to be supplied

Dermatological preparations should preferably be dispensed in a limited number of standard amounts. For semisolids 5g, 15g, 30g, 50g and 100g are suitable standard amounts. For liquid preparations 50ml, 100ml, 200ml and 500ml are suitable.

It is often very difficult to determine how much of a certain preparation a patient needs. For a very limited number of preparations one standard amount needed per patient for a complete cure can be determined. This is for example the case for lindane cream. If the amount needed can be estimated, it is included in each preparation monograph.

In other cases the amount needed for a particular patient should be estimated from the dose and duration of the therapy and the area of skin involved. Standard amounts needed to treat a particular part of the skin two times daily for one week are given in table 1.1. The amounts are rounded off into the nearest standard amount.

table 1.1:
amounts of preparation needed to treat the stated part of the body two times daily for one week.

part of body	cream/ointment/paste	liquid preparation
face	5 - 15 g	100 ml
hand	15 - 50 g	200 ml
arm	50 - 150 g	200 ml
leg	100 - 300 g	200 ml
trunk	200 - 500 g	500 ml
whole body	500 - 1500 g	500 ml

Creams are generally more economic than ointments or pastes. The quantity of an ointment necessary for a specific treatment is 1.5 - 2 times as much as the quantity of a comparable cream for the same treatment. The quantity of a paste necessary for the same treatment is 2 - 3 times as much.

For certain preparations a maximum dose is indicated in the monograph. The amount supplied should always be below this maximum dose.

Children have a smaller skin surface, and smaller quantities are usually sufficient. The strength of preparations for children, the frequency of application and the duration of therapy in children are usually the same as those for adults. However, certain dermatological preparations may be more dangerous to children. If this is the case, the need for treatment and the optimal dose should be very carefully evaluated, and special precautions may be necessary. Information on this subject is included in the preparation monographs whenever relevant.

4 packaging

Packaging is essential to protect the preparation from adverse environmental influences. In the monographs on the preparations and the raw materials the optimal package is specified. However, the optimum is not always possible. If suboptimal packages are used, the shelf life will be shorter.

In general, the following packages are suitable for dermatologicals:
1. glass or polyethylene bottles for fluids;
2. polyethylene jars for semisolids.

The use of jars made of glass is also possible but these are a little more expensive, heavier, and more fragile.

The jars should have a wide opening so that the contents can be stirred when they have

Calamine lotion **batch quantity: 1000 ml.**

figure 1.1

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. zinc oxide	200 g				
2. bentonite	30 g				
3. trisodium citrate (.2H2O)	5 g				
4. glycerine	50 ml				
5. phenol liquified	5 ml				
6. water	to 1000 ml				
7. dark colored glass bottle of 1000 ml	1				

Preparation

- Heat 1 litre water to the boil and allow to cool. Use this water for the preparation. — water boiled?
- Calibrate the glass bottle for 1000 ml. — calibration control:
- Dissolve the trisodium citrate in 700 ml of water. — completely dissolved?
- Mix the zinc oxide with the bentonite in a mortar.
- Triturate this zinc oxide/bentonite mixture with the glycerine and 200 ml of the citrate solution.
- Add the rest of the citrate solution and mix until completetly homogeneous. — homogeneous?
- Add the liquified phenol and mix.
- Bring the mixture into the calibrated bottle.
- Rinse the mortar with a little water.
- Add sufficient water to produce 1000 ml of lotion and mix until homogeneous. — total volume: homogeneous?

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°
protect from direct sunlight
shelf life: 3 months
expire date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials — correct?
- package — well closed?
- label — correct expire date?

batch released on (date):
by name:

model of label for stock:

for external use only
calamine lotion
batch number/date
do not use after: (date + 3 months)
protect from direct sunlight
shake well before dispensing or use

model of label for the patient:

dispensing unit and date
for external use only
calamine ..... ml
name of patient
shake well before use
paint the lotion on the skin ..... times daily
and allow to dry; do not cover.
do not use after (dispensing date + 10 days)

become inhomogeneous, and so that the jars can be easily cleaned when they are to be reused. Frequently reopening and stirring the contents of jars will increase the risk of microbial contamination. Therefore we have selected preparations with a good physical and microbial stability. However, some type of physical instability, e.g. sedimentation of suspensions and bleeding of petrolatum, cannot always be avoided.

The introduction of a deposit system could be considered to ensure the return of empty jars and bottles.

Some preparations have to be protected from light. This can be done by packing them in a suitable package, but storing them in the dark is just as effective. They can also be wrapped in a piece of dark paper or cloth.

Some preparations, for example dithranol cream, require an airtight container. Glass containers with a tightly fitted screw cap are the most suitable. Zinc oil reacts with certain plastics, including polyethylene, therefore this preparation should be packed in glass containers.

Collapsible tubes have certain advantages. They do provide adequate protection against microbial contamination and light and they are airtight. But they are expensive and not reusable. If a preparation gets inhomogeneous this cannot be seen and stirring of the contents is impossible. Therefore collapsible tubes are not generally suitable for use in hot climates.

5 labelling

It is essential that all drugs, preparations or raw materials, are adequately labelled. Labelling raw materials is generally done by the producer of the materials. For optimal stock control it is advisable to provide raw materials and preparations with a label stating the date of receipt.

Labelling preparations should be done immediately after packaging. If the preparation will be stocked, the label should contain the following information:

- full name of the preparation;
- preparation date;
- expiry date ("should not be used after....."");
- storage conditions;
- necessary dispensing information, such as "shake before dispensing or use" or "mix before dispensing or use";
- warnings in cases of toxic or hazardous preparations.

If a preparation is dispensed, the following information must be given on the label:

- name of the patient;
- "for external use only";
- name of the preparation;
- dose and instructions for use, pictograms may be necessary for patients who cannot read;
- dispensing date;
- expiry date ("do not use after....."");
- warnings in cases of toxic or hazardous preparations.

6 storage

For the storage of drugs and preparations a cool, dark and dry place is always best. This does not mean, however, that all drugs have to be kept in a refrigerator, or that special storage rooms are always necessary. The following general recommendations can be given:

a. a dark, cool and dry place is preferable;
b. the stock room should be kept clean and free from insects, rodents etc.;
c. drugs should be stored orderly:
   - to avoid accidents, drugs for external use should be kept apart from other types of drugs such as tablets,
   - all drugs should be properly labelled,
   - all drugs should be stored in alphabetical order,

- new articles should be put behind the old stock, so that the old stock is used first (first in, first out),

d. secure the drugs against theft.

7 stock control

Stock control of medicines is as difficult as it is important. A certain amount of medicines should be held in stock in order to be able to dispense them on demand. On the other hand, if the stock is too big, the medicines may be stored too long and they may get out of date.

The shelf lives given in the preparations chapter should be divided into two parts; the shelf life before dispensing, at the production unit, the medical store and the dispensary, and the shelf life after dispensing, at the patients home or at the hospital. The shelf life needed at the patients home depends on the dosage regimen and the duration of therapy. It can only be estimated approximately. Medicines should, therefore, be dispensed far enough before their expiry date to allow for a reasonable shelf life at the patients home.

The amount of medicines in stock should be large enough to be able to dispense the medicines until new stock arrives or until it can be prepared. But the stock should be small enough to ensure that all the medicines are dispensed and used before their expiry date. It is, therefore, often better to produce smaller amounts of medicines at a time and to do this more often.

To facilitate stock control, keeping records of the amounts of medicine prepared and dispensed is essential. If this is done for a longer period of time, one will be able to estimate the optimal stock on the basis of these records.

New stock should always be stored behind old stock, so that the old stock is dispensed first. In the preparations and raw materials monographs an indication is given on the consequences of the use of out of date materials and preparations. This does not mean that out of date drugs may be dispensed, even if there are no risks associated with their use and even if the shelf lives given are quite arbitrary. One should always try to comply with expiry dates. Out of date preparations should only be used if there is a pressing need to do so.

8 safety precautions

Some of the materials used in the preparations of this formulary are highly active, toxic, irritating or staining. These materials should be handled with great care. Contact with the skin and the eyes should be avoided while handling these materials. If they are available gloves may be worn. It is also advisable to wear safety goggles or one's own pair of spectacles. Take away spoiled materials immediately.

It is advisable to have someone else control all calculations, weighings and measurements of such materials. Dangerous materials used in the preparations of this formulary include coal tar, dithranol, gentianviolet, lindane, iodine, para aminobenzoic acid, potassium permanganate, phenol and silver nitrate. More specific information on the hazards of these materials can be found in the raw materials monographs in chapter 6.

9 temperatures

Temperatures in this formulary are given in degrees Celsius (°C). In some countries degrees Fahrenheit are still used. To calculate the temperature in degrees Fahrenheit if degrees Celsius are given, multiply by 9/5 and add 32 (formula I). To calculate degrees Celsius if degrees Fahrenheit are given subtract 32 and multiply the result by 5/9 (formula II).

$$°F = °C \times 9/5 + 32 \qquad I$$

$$°C = (°F - 32) \times 5/9 \qquad II$$

Example 1. You want to check the temperature of a solution with a thermometer having a Fahrenheit scale. The temperature should be 70°C. The Fahrenheit scale should read 70 x 9/5 + 32 = 126 + 32 = 158°F.
Example 2. You measure a room temperature of 95°F, but you want to know the temperature in degrees Celsius. This is (95 - 32) x 5/9 = 63 x 5/9 = 35 °C.

10 weights and measures

In this formulary the SI unit system is used. Weights are expressed in grams (g) and volumes in milliliters (ml). To prevent mistakes only this unit system should be used. If weights and measures are only available in other unit systems which are still used in a number of countries, these may be used. All amounts stated should then be changed into the other unit system. Make sure you know exactly how to do this and ask somebody else to check your calculations in order to prevent errors.
* Volume units:
The American system of volume units is based on the US gallon:
- 1 US gallon = 3785 ml.
- 1 US quart = 1/4 US gallon = 946 ml
- 1 US pint = 1/8 US gallon = 473 ml
- 1 US gill = 1/32 US gallon = 118 ml
- 1 US fluid ounce = 1/128 US gallon = 29.6 ml
- 1 US fluid dram = 1/8 US fluid ounce = 3.7 ml
- 1 US minim = 1/60 US fluid dram = 0.06 ml

British countries use the same system, but refer to the imperial gallon which is equivalent to 4543 ml. The corresponding values are:
- 1 imp. gallon = 4543 ml
- 1 imp. quart = 1136 ml
- 1 imp. pint = 568 ml
- 1 imp. fluid ounce = 35.5 ml
- 1 imp. fluid dram = 4.4 ml

The other way around, the corresponding values for one millilitre are:
- 1 ml = 0.00026 US gallon = 0.0021 US pint = 0.034 US fluid ounce = 0.27 US fluid dram = 16.2 US minim.
- 1 ml = 0.00022 Imp. gallon = 0.0018 Imp. pints = 0.028 Imp. fluid ounce = 0.23 Imp. fluid dram = 13.5 Imp. minim

Check whether volume units are in imperial or US gallons before calculating.

* Weight units:
Two unit systems for weights are still in use in some countries:
- 1 pound lbs (avoirdupois) = 454 g
- 1 ounce = 1/16 lbs = 28.4 g
- 1 draw = 1/16 ounce = 1.8 g
- 1 grain = 1/7000 lbs = 0.065 g

- 1 troypound (apothecaries) = 373 g
- 1 troyounce = 1/12 troypound = 31.1 g
- 1 pennyweight = 1/20 troyounce = 1.6 g
- 1 grain = 1/5760 troypound = 0.065 g

The other way around, 1 gram is equivalent to:
1 g = 0.035 ounce (avoirdupois) = 0.564 draw = 15.4 grains.
1 g = 0.032 troy ounce (apothecaries) = 0.643 pennyweights = 15.4 grains.
The symbol for grain is gr, for gram g. Always use the right symbol for each of them to prevent mistakes. Be careful to check to which system pounds and ounces refer.
An example: you want to measure 100 ml. with a measure calibrated in fluid ounces (US): 100 ml = 100 x 0.034 = 3.4 US fluid ounces.

2 Good manufacturing practices

Basic standards of good manufacturing practice for local production units in tropical countries

1 personnel

1.1 Each unit should have a responsible person approved by the authorities. Preferably, there should be separate heads for manufacture and control. The number of employees should be sufficient in order to ensure the quality of the product and to comply with necessary instructions.

1.2 All personnel should be properly trained and instructed with respect to their tasks.

1.3 Immediately upon appointment all personnel should be given written instructions concerning:
- the organization of the unit;
- rules and formats of labelling;
- procedures in case of mistakes and problems;
- safety precautions to be taken when handling toxic or dangerous materials, emergency rules (fire etc.);
- personal hygiene (cf. 2. hygiene).

All employees should sign a written statement declaring that they have taken notice of these instructions.

2 hygiene

2.1 High standards of personal cleanliness should be observed by all people concerned with production processes.

2.2 Hand-washing and hygienic drying facilities should be available to, and used by, manufacturing personnel (cf. 3. premises). Direct contact should be avoided between the operator's hands and starting materials, intermediates and products.

2.3 All personnel entering production areas should wear adequate clothing. Clothing should be clean and should not be worn outside the production unit.

2.4 Personnel should report infections and skin lesions to the staff, and a defined procedure should be followed when such reports have been made.

2.5 Eating, drinking, chewing and smoking should be confined to a separate room, which is not used for other purposes.

3 premises

3.1 Premises should be of a suitable construction and should be adequately adapted to and be of a sufficient size for their intended use.

3.2 Premises should be suitably illuminated and ventilated. The working areas should have a sufficient size in order to minimize the risk of mix-ups and cross-contamination.

3.3 The premises should include adequate accommodation for changing clothes, washing and toilet purposes.

3.4 The premises should be constructed and equipped so that they can be easily cleaned and, if necessary, disinfected. Cleaning and disinfection should occur according to written instructions. The premises should be kept free from insects, pests, rodents or other animals.

4 equipment

4.1 All equipment used in manufacture or quality control should be regularly inspected to ensure its proper functioning.

4.2 All equipment must be safe. Operating- and cleaning instructions should be in the immediate vicinity of the apparatus.

4.3 Weighing and measuring equipment should be accurate and, if necessary, should be regularly calibrated.

4.4 Manufacturing equipment should be suitable for its purpose, easy to clean and non reactive to the materials employed.

5 manufacturing procedures

5.1 large scale production

5.1.1 There should be a master formula stating components and procedures for manufacturing and quality control for each product. Each batch should be produced according to a batch manufacturing record. This batch manufacturing record is a true copy or authorized transcript of the master formula. All relevant information obtained during the production process (measurements, readings and batch numbers) should be recorded on this batch manufacturing record. All batch manufacturing records should be filed for a specified period of time.

5.1.2 All components, intermediates and products should be identifiable throughout the whole production process.

5.1.3 All components must comply with their particular specifications and be labelled with the name designated in the specification before being released for use. The same name should be used in the master formula and batch manufacturing record.

5.1.4 Liquids, creams and ointments should be manufactured in such a way that microbial contamination is avoided.

5.1.5 Water used for the production of topical preparations should be of at least potable quality and have a low microbial count.

5.1.6 All finished products should be identified by labels that should bear at least the following information:

- name of the unit;
- name of the product as given in the master formula;
- batch number;
- expiry date.

5.2 extemporaneous preparation and dispensing

5.2.1 There should be a master formula stating components and production procedures for each preparation.
All relevant information obtained during the production process should be recorded, preferably on the doctor's prescription. These records should be filed during a specified period of time.

5.2.2 All components, intermediates and products should be immediately processed or be identifiable until processed.

5.2.3 Liquids, creams and ointments should be manufactured in such a way that microbial contamination is avoided.

5.2.4 Water used for the production of topical preparations should be at least of potable quality and have a low microbial count.

5.2.5 Finished products that are not immediately handed out to the patient should be identified by labels that should bear at least the following information:
- name of the unit;
- name of the preparation;
- date of production;
- name of the patient.

5.2.6 When preparations are delivered to the patient measures should be taken to ensure that:
- the right preparation is delivered to the right patient in the right quantity;
- the preparation complies with all legal requirements;
- the patient is properly instructed on the way of administration of the drug. Personnel assigned to this task should be properly trained.

3 Basic methods

1 weighing

Measurements of solids should be done by weighing. Measurements of solids by volume is not accurate enough in drug preparation. Measurements of liquids, however, is generally done by volume, as this is the easiest and most efficient way. But liquids may be measured by weight too. To calculate the weight of a stated volume of a liquid, use formula I. Formula II can be used to calculate the volume of a given weight. The density d is different for each material. Refer to the chapter on raw materials for these constants. The density is dependent on the temperature. The values given in the chapter on raw materials are valid at 20°C. They should not be used for calculations at temperatures below 10 or above 30°C.

weight = d x volume I

volume = weight / d II

To ensure accurate weighing, follow these general rules:

* Use a balance suitable for weighing the stated quantity. The minimal weight that can be accurately measured with a balance can be determined by multiplying the smallest scale unit by 20. Do not try to weigh quantities greater than the capacity of the balance. Check that the balance and the weights are calibrated for the SI unit system. If they are not, use the conversion factors in chapter 1.
* Before weighing, check that the balance:
  - is clean;
  - is in a completely level position;
  - is in a place free from draught;
  - is set to zero or tared.

  Also make sure the balance arm can move freely. This can be checked by touching the balance pan with the forceps.
* Always make sure that the balance is in the down or resting position before transferring materials or weights to or from the pans.
* Never weigh pharmaceutical materials directly on the balance pan. Use a piece of paper for solids, waxed paper for semisolids, and an appropriate vessel for liquids. The vessel used for liquids should, of course, be cleaned after each weighing.
* Use a suitable spatula for the transfer of materials to the balance pan. Take care not to spill any material. Clean immediately if you spill any material. The spatula should be cleaned after each weighing.
* Some pharmaceutical materials are corrosive or aggressive. Special containers and spatulas are sometimes needed. This is indicated in the chapter on raw materials.
* Always use forceps to transfer weights. Never touch weights with your fingers. Put weights back into the weight drawer or into their case immediately after use. Close the weight drawer immediately. This avoids corrosion and contamination of the weights.
* If a solid that has to be dissolved in a liquid has been weighed, it may be washed of with this liquid.
* Clean the balance thoroughly after use.

1.1 weighing with a double pan balance:

1. Place a piece of paper, waxed paper or a suitable container on the right hand pan.
2. Tare the balance by placing an equivalent piece of paper or container on the left hand pan. Weights or other tare equipment may also be used. Always use the right hand pan for the material that is to be weighed, and the left hand pan for tares and weights.
3. Put weights equivalent to the stated quantity on the left hand pan.
4. Transfer the material to be weighed to the right hand pan. Add enough material to balance the pans.

1.2 weighing with a single pan balance:

1. Set the balance to zero.
2. Place a piece of paper, waxed paper or a suitable container on the pan.
3. Read the scale and note the reading (x grams). Always read the scale at eye level.
4. If y grams are to be weighed add material until the scale reads x plus y grams.

2 measurement of liquids

Liquids are generally measured by volume. They may be measured by weighing (see above). Measurement by volume can be done with measures, pipettes, with a dropper or with syringes. The first method is used for larger volumes, the other methods are used for small volumes.

There is an essential difference between pipettes and other types of volumetric glassware, such as volumetric flasks. Pipettes are designed to deliver a certain volume, and they are used to transfer the required amount of liquid from one container to another. Volumetric flasks have an exactly known capacity. They are generally used to make a solution of a certain concentration. Graded cylinders are frequently used for both purposes. However, when they are used to transfer liquids with a high viscosity, a substantial amount may remain in the cylinder; thus the error may be large.

2.1 measurement with measures:

To ensure accurate measurements, follow these rules:

* Select a measure of a suitable size. Pharmaceutical measures show no scale lower than the minimum volume that can be measured accurately with them.
* Make sure the scale of the measure is in milliliters, not in centiliters, pints, gallons or any other unit. If it is in other units, use the conversion factors mentioned in chapter 1.
* Always read the scale at eye level, at the bottom of the liquid surface (meniscus) (see figure 3.1). If the reading of the scale is difficult, hold a piece of dark coloured paper behind the measure.

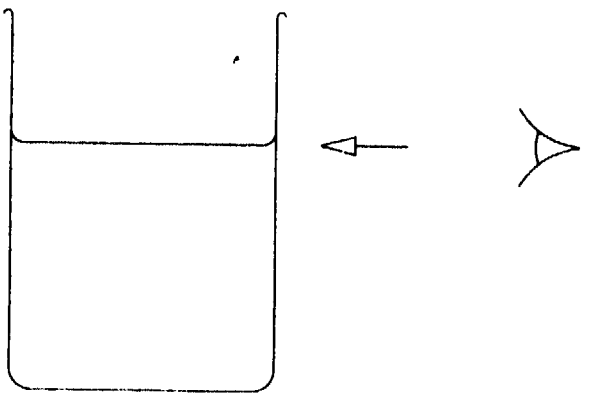

figure 3.1:
reading of the scale of volumetric glassware

* Make sure no liquid remains in the measure. It may take some time for the liquid to flow out completely, particularly with viscous liquids. For water and aqueous solutions keep the measure top down for 15 seconds after all the liquid has flown out, and 2 minutes for syrups and oils.
* Measures should be cleaned and dried after each measurement. Measures should not be used while still wet.
* To prevent contamination of measures with dust, they should be kept upside down, preferably in a cupboard.

2.2 measurement with pipettes:

Pipettes may be used for accurate measurements of small volumes. Pipettes are calibrated for one specific liquid at one specific temperature. Usually, this is water at 20°C. They may be used for the measurement of other liquids but will be less accurate in these measurements. It may be very difficult to clean the pipette after the measurement of oils. To ensure accurate measurements, follow these rules:

* Always use a pipette with a suitable volume.
* Make sure the scale is in milliliters, not in centiliters, pints or other units.
* Read the scale at eye level at the bottom of the liquid surface (meniscus) (see figure 3.1). If you find it difficult to read the scale, hold a piece of dark coloured paper behind the scale.
* Liquid is drawn into the pipette through the application of a slight vacuum. A rubber suction bulb should preferably be used to draw liquid into the pipette (see figure 3.2). Mouth suction should never be used with dangerous or toxic liquids.

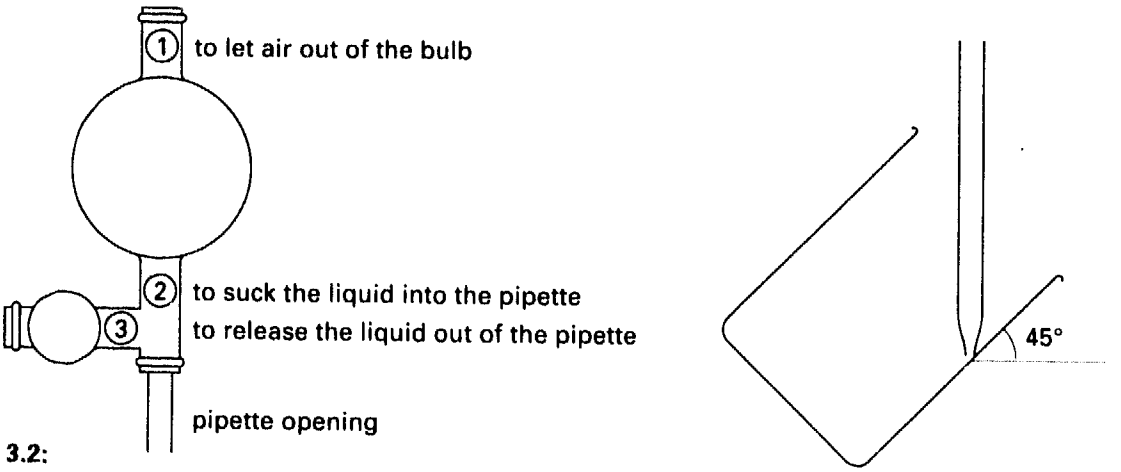

fig. 3.2:
the use of pipettes

Measurements are done as follows:

1. Draw a small volume of the liquid to be measured into the pipette and thoroughly wet all the internal surface of the pipette. Allow the liquid to drain and discard it.
2. Carefully fill the pipette to a level slightly above the graduation mark.
3. Quickly replace the bulb (or mouth) with a forefinger to stop the liquid from flowing out.
4. Make sure there are no air bubbles in the fluid or on the fluid surface.
5. Wipe the outer surface of the pipette clean.
6. Hold the tip of the pipette against a glass vessel and allow the liquid to flow out until the bottom of the liquid surface just touches the graduation mark. The best way to control the flow of liquid from the pipette is with a slightly wet forefinger.
7. Place the tip of the pipette against the inner wall of the receiving container, holding the pipette in a vertical position and the container at an angle of about 45° from vertical (see figure 3.2).
   Allow the liquid to flow out.
8. When the free flow ceases, rest the tip against the wall of the container for an additional 15 seconds.
9. Rinse the pipette thoroughly after use.

2.3 measurement with a dropper:

A dropper may be used to measure small quantities of a liquid. Any sort of apparatus that produces droplets of uniform size may be used for this purpose. Pasteur pipettes are a good example of these, a dropper from an eyedrop bottle is another example. The dropper should be calibrated for the liquid that is to be measured with it. This means the exact weight or volume per droplet is known (or the other way around, that the number of drops per gram or millilitre is known).

To calibrate a dropper fill it with the liquid for which it should be calibrated. The apparatus should be clean and dry before filling. Count the number of drops needed to obtain a standard weight or volume that can be accurately measured (for example one gram or 10 milliliters). Calculate the weight or volume per droplet with formula III or IV.

weight per droplet	= weight obtained / number of droplets	III
volume per droplet	= measured volume / number of droplets	IV

To measure a liquid with a dropper, fill it with the liquid that should be measured. The apparatus must be calibrated for that particular liquid. Calculate the number of drops that correspond to the weight or volume needed with formula V or VI. Drop until the calculated number of drops is obtained. Clean and dry the apparatus immediately after use.

number of droplets	= weight needed / weight per droplet	V
number of droplets	= volume needed / volume per droplet	VI

3 making up to volume or weight

3.1 making up to volume

Making up to volume means adding a liquid vehicle until a required volume is obtained. This may be done in a measure of suitable size, or in a calibrated vessel. All kinds of vessels may be used. To calibrate, fill the vessel with the required volume of water and mark the level, preferably on the outside. Use recently boiled and cooled water to prevent contamination of the vessel.

3.2 making up to weight

Creams and ointments often require the addition of a vehicle or raw material until the required weight is obtained, which is called making up to weight. Weighing may be done in the vessel in which the product is prepared, provided the total weight of vessel and product does not exceed the capacity of the balance. The empty weight of the vessel and mixing device should be determined before the preparation is started.

4 size reduction and sieving of solids

Size reduction of solids may be necessary if a fine powder is required and only crystals or a coarse powder are available. In dermatological preparations, a particle size of less than 90 μm is preferred. Many raw materials already have a suitable particle size, but some do not and require size reduction. Some materials require special precautions during grinding and sieving. In the preparations section grinding and sieving instructions are included whenever necessary.

Grinding may be done before mixing (dry grinding) or during mixing (wet grinding) with the liquid or semisolid. If sieving is necessary, only dry grinding is possible. Raw materials should preferably be grounded and sieved before the required quantity is weighed, because some loss of material usually occurs during these procedures.

4.1 grinding before mixing:

Place the solid material in a stone mortar with a rough wall of a suitable size and grind with a pestle. During grinding remove particles from the wall of the mortar with a suitable scraper from time to time. The material should preferably be sieved after grinding.

4.2 grinding during mixing:

Place the solid material in a stone mortar with a rough wall of a suitable size. Triturate this with an approximately equal amount of fluid or semisolid using a pestle. To triturate means to rub between the wall of the mortar and the pestle very carefully. Remove the mixture from the wall of the mortar several times during grinding, using a suitable scraper. After wet grinding sieving is not possible. Smear a small amount of the mixture on a piece of glass or dark material to check for any remaining lumps.

4.3 sieving:

Sieves were formerly characterised by the number of meshes per inch, the mesh number. Nowadays, the sieve number is used to characterise sieves. The sieve number indicates the nominal aperture size of the meshes in µm. Table 3.1 relates sieve numbers to mesh numbers. For dermatological preparations a particle size smaller than 180 µm is necessary, but a particle size smaller than 90 µm is often preferred.

table 3.1:
sieve numbers and mesh numbers

sieve number	mesh number
250 µm	60 /inch
180	85
150	100
125	120
106	150
75	200

Sieving is used to separate fine powder from coarse powder or lumps. The powder is placed on a sieve with a suitable opening size. The material is gently stroked with a rubber stopper or other suitable equipment. A brush is sometimes advised, but brushes are very difficult to clean after use and they may cause cross-contamination.

The fine powder passing the sieve should be collected in a suitable container or on a clean sheet of paper.

Mixtures should always be remixed after sieving as separation due to the sieving procedure may occur.

Sieving should always be done before weighing the stated quantity.

5 mixing of ingredients

5.1 mixing of miscible liquids

Miscible liquids can be easily mixed by shaking or stirring. Care should be taken not to introduce too much air.

5.2 dissolving a solid in a liquid

A good and convenient procedure to prepare a solution is as follows: weigh the required quantity of the solid in the vessel in which the solution will be prepared, and add the liquid to this vessel. Mix by stirring or by shaking until dissolution is complete. Take care not to introduce too much air into the solution. Check for complete dissolution. This is very easy if the solution is prepared in a glass vessel. If the solid is added to the liquid, take great care to transfer all of the solid.

In certain cases gentle heat may be applied to speed up dissolution. It should never be used to increase the solubility, because crystallization will occur upon cooling if this is done. Gentle heat should not be applied if the solid or liquid is instable. If gentle heat can be applied, this is indicated in the preparations monograph.

5.3 mixing of solids

Mixing of solids should preferably be done in a stone mortar with a rough wall, by rubbing the solids together between the pestle and the wall of the mortar. This is called trituration. Use a mortar of a suitable size for optimal mixing efficiency and minimal spoilage risk. Mixing is most efficient if equal amounts of solids are mixed. If a relatively small amount of a solid A is to be mixed with a large amount of solid B, this can most efficiently be done by first mixing A with an equal amount of B. The remaining part of B is added gradually. During mixing, remove particles from the wall of the mortar with a suitable scraper from time to time. Use a mortar of suitable size for optimal mixing efficiency and minimal spoilage risk.

A mixture of solids may get inhomogeneous during transport or during sieving. If you have any doubt, rehomogenize before using a powder mixture.

5.4 mixing a solid with a semisolid

The mixing of a solid with a semisolid ointment base is a very common operation. It should preferably be done in a mortar. The solid is first triturated with an equal part of the semisolid, because equal parts mix best. Triturating means rubbing between the pestle and the mortar wall carefully. The rest of the semisolid should be added gradually. During mixing, remove particles from the wall of the mortar with a suitable scraper from time to time. Use a mortar of suitable size for optimal mixing efficiency and minimal spoilage risk.

In rare cases, the application of gentle heat is needed to ensure efficient mixing. If this is the case, it is indicated in the preparations monograph.

5.5 mixing of fatty substances

Fatty substances are usually mixed by melting them together over gentle heat in a metallic mortar with a plastic pestle. The melted material is stirred until homogeneous, stirring is continued gently until the mixture is cold. Semisolid materials may sometimes be mixed without melting.

5.6 mixing a liquid and a semisolid

Mixing of a liquid and a semisolid is usually done without melting. The liquid should be added to the semisolid by small quantities at a time. Mix well after each addition.

6 heating

The application of heat is often required. Two types of heat are distinguished, heat and gentle heat.

Heat is used primarily for boiling water. Any heat source can be used for this purpose, such as gas, petroleum, wood, coal, electricity etc. Gentle heat is used for melting fatty substances and speeding up dissolution. Normal heat sources often are unsuitable, because there is a great risk of overheating the material. A water bath is most suitable for these purposes. On a water bath the material is heated indirectly by hot water. Overheating is prevented because water cannot reach a temperature of more than 100°C. Simple pans filled with water are suitable as a water bath. It may be very handy to put the lid on the pan upside down; this produces a warm surface on which materials can be very gently heated.

7 sterilization

Heat is also used to sterilize solutions. Sterilization is important to reduce the number of micro-organisms in solutions that are used on wounds, or that are infused. To sterilize solutions, they should be maintained at a temperature of 121°C for 15 minutes. This is only possible under

pressure. Sterilization is usually done in an autoclave with adequate facilities to check both the temperature and the pressure. If autoclaves are not available, a pressure cooker may be used, provided it has a facility to check the temperature or the pressure. To sterilize a solution, proceed as follows:

1. Fill the autoclave or pressure cooker with sufficient water. A minimum water level should be maintained throughout the sterilization procedure.
2. Bring the solutions that are to be sterilized into the autoclave or pressure cooker. The solutions should be packed in their final package. The package must be able to resist a temperature of 121°C. Glass is suitable. If the package is able to resist high pressure, close it tightly. If the package is not able to resist high pressure, the closure should be loosely fitted.
3. Close the autoclave or pressure cooker.
4. Open the steam valve.
5. Heat until the water boils. The temperature is 100°C, and the autoclave or pressure cooker is steaming.
6. Allow to steam for 10 minutes and then close the steam valve. The pressure rises to 2 bar (approximately 2 atmosphere) and the temperature to 121°C.
7. Maintain the autoclave or pressure cooker at this pressure and temperature for 15 minutes.
8. Switch of the heat source and allow to cool to 80°C. Open the steam valve, then open the autoclave, close the packages and take the sterilized solutions out.
9. Mark the packages clearly.

4 Indications for preparations

This chapter contains a list of skin diseases that can be treated with the preparations of the formulary. Included are the most common skin diseases, not the very rare that need specialized treatment. The order in which the preparations are listed indicate their rank of choice. In the monographs of the preparations in chapter 5 the reasons for this ranking are given briefly. More detailed information on the backgrounds of choices of preparations and their effectiveness is given in chapters 10, 11 and 12 in part II of this book.

acne	salicylic acid solution sulphur lotion
bullous dermatoses	potassium permanganate solution strong corticosteroid preparation + indifferent vehicle
burns	silver nitrate solution silversulphadiazine cream
corns and calluses	salicylic acid ointment
dermatitis/eczema	calamine lotion zinc oil hydrocortisone cream or ointment tar cream, solution or paste strong corticosteroid preparation + indifferent vehicle
disinfection e.g. tools for surgery	industrial methylated spirit 70%
disinfection intact skin	iodine tincture or solution chlorhexidine solution 1%
disinfection wounds	iodine solution or tincture chlorhexidine solution 0,1%
dry skin	petrolatum emulsifying ointment urea cream or ointment
fungal infections e.g. candidiasis e.g. athlete's foot	gentianviolet solution miconazole preparation nystatin preparation Whitfield's cream or ointment
ichthyosis	petrolatum emulsifying ointment urea cream or ointment

immunological disorders	hydrocortisone cream or ointment strong corticosteroid preparation + indifferent vehicle
leprosy dry skin due to	petrolatum emulsifying ointment
leg ulcers e.g. in leprosy	gentianviolet solution potassium permanganate solution zinc paste
parasitic infections scabies/pediculosis	lindane cream benzylbenzoate emulsion sulphur cream or ointment
photodermatoses	zinc paste para aminobenzoic acid solution or cream
pigmentary disorders vitiligo	strong corticosteroid preparation + indifferent vehicle
pityriasis versicolor	sodium thiosulphate solution sulphur cream or ointment
protection	zinc paste petrolatum
pruritus	calamine lotion hydrocortisone cream or ointment
psoriasis	salicylic acid ointment strong corticosteroid preparation + indifferent vehicle tar cream, solution or paste dithranol paste or cream
pyoderma	gentianviolet solution potassium permanganate solution
sunscreen agents	para aminobenzoic acid solution or cream zinc paste
tinea	Whitfield's cream or ointment miconazole preparation
viral diseases common warts	salicylic acid ointment

5 Preparations

This section contains monographs on all the preparations of this formulary. The monographs are all written in the same way. They intend to give the general information necessary to prepare and dispense the preparations.

The following headings are included:

● Preparation

synonyms

contains: composition of the preparation

● Formulation

all raw materials and the amounts needed.

preparation:

- preparation methods are given; for more information the general notes and the chapter on basic methods can also be consulted.

packaging:

- general packaging instructions;
- special packaging instruction for dispensing from stock;
- amount needed per patient if an estimate is possible, see also chapter 1.3.

storage:

- optimal storage conditions; the term "should" indicates requirements that are absolutely necessary, whereas "should preferably" indicates storage conditions that are strongly recommended;
- maximum storage period (total storage, including storage at patient's home);
- possible changes during storage and their consequences;
- signs of degradation (if any);
- risks of using an out of date preparation.

● Therapy

- for external use only;
- general information on therapeutical properties, related drugs etc., refer also to the list of indications. For more information see chapters 10, 11 and 12 in part II of this book.

dose:

- recommended dose and, if relevant, duration of therapy.

instructions for use:

- all relevant information the health worker should tell the patient to enable correct use.

precautions:

- all relevant precautions patients or health workers should take to ensure the preparation is used safely.

pregnancy/lactation:
- available information on the possible risks for the unborn or newborn child, when a preparation is used by the mother.

side effects:
- information on local and systemic side effects and irritation or sensitization potential of the preparation.

intoxication:
- any information on signs that may indicate systemic intoxication resulting from external use;
- information on the treatment of intoxication resulting from accidental ingestion (only included for liquid preparations);
- any other relevant information.

● Additional information

This part contains miscellaneous additional information. The following information may be included:

* information on the origin of the formula;
* information on the reason for using particular raw materials;
* information on alternative ingredients if certain raw materials are not available;
* if relevant: information on resistance;
* if relevant: information on non drug treatment;
* information on the necessary precautions if large amounts of the preparation are prepared for stock;
* information on other strengths used.

● BASIC CREAM

contains: 15% lanette wax, 35% paraffins, 0,15% methylparaben and water.

● Formulation

lanette wax SX		15	g
liquid paraffin		12,5	g
petrolatum		22,5	g
methylparaben		0,15	g
water	to	100	g

preparation:

1. Melt together lanette wax, liquid paraffin and petrolatum over gentle heat and mix.
2. Heat this mixture to approximately 70°C.
3. Heat sufficient water to the boil. Dissolve the methylparaben in 50 ml of this boiling water. Allow the rest of the boiled water to cool.
4. Allow the methylparaben solution to cool to approximately 70°C.
5. Add this solution to the fat mixture (2.) at a temperature of approximately 70°C and mix.
6. Stir gently until cold.
7. Add enough recently boiled and cooled water to produce 100 grams of cream. Mix until completely homogeneous.

packaging:

- Basic cream should be packed in a well closed container, which prevents the evaporation of water and the contamination with micro-organisms.
  The package should allow stirring of the cream.
  Basic cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, basic cream should be mixed until homogeneous before dispensing from stock.

storage:

- The cream should preferably be stored below 40°C.
- The cream should preferably be used within 3 months.
- Out of date creams risk being contaminated with micro-organisms, which may cause infections.
- Basic cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not well closed, water may evaporated during storage. This results in an emulsifying ointment with a certain amount of water remaining. If active ingredients are incorporated in the cream, they will be more concentrated, but the concentration will never be more than twice as strong. The changed properties of the cream should be taken into account whenever out of date creams are used.

● Therapy

- For external use only.
- Basic cream is used as a vehicle for a number of active ingredients. It has a relatively high fat content. The cream is easily washed away with water, and therefore it is suitable for use on hairy parts of the skin.
  Basic cream is not very occlusive, it may even have a slight drying effect on the skin. Basic cream is appropriate for the use as an indifferent preparation in intermittent treatment with strong corticosteroid preparations.

dose:
- Apply in a thin layer several times daily.

instructions for use:
- The cream should be applied in a thin layer. Excessively thick layers may cause some occlusion. Occlusion is unwanted in most cases as it may result in secondary infections and exacerbations of various skin diseases.
- If the cream is inhomogeneous, it should be mixed before use.

pregnancy/lactation:
- Harmful effects resulting from external use of basic cream have not been reported.

side effects:
- Side effects are rare. Sensitization due to methylparaben may occur, but is rare with the concentration used in this cream. Sensitization due to yellow petrolatum may occur, but is rare.
  Irritation due to lanette wax has been described. Inferior qualities of white petrolatum can also cause irritation. If sensitization or severe irritation reactions develop, stop the use of this preparation and do not use it again.

● Additional information

* The formula for basic cream is modified from the one given in the British Pharmacopoeia for aqueous cream. Aqueous cream of the British Pharmacopoeia contains 30 grams of emulsifying ointment, 1 gram of phenoxyethanol and 69 grams of water. The basic cream we recommend is more stable at high temperatures than the original formula from the British Pharmacopoeia.

* 35% liquid paraffin or 35% petrolatum may be used instead of the mixture of the two. The mixture, used in the formula above, results in the most stable cream, and is therefore preferred.

* Methylparaben can be substituted by various other preservatives, for example 10% propylene glycol or 1% phenoxyethanol. However, methylparaben is preferred because of its favourable cost/effectiveness and risk/effectiveness balances.

* An easier way to prepare basic cream is using emulsifying ointment instead of lanette wax, liquid paraffin and petrolatum. The formula than reads: emulsifying ointment 50 g; methylparaben 0.15 g; water to 100 g. The preparation method remains essentially the same. From a pharmaceutical point of view, it is better to use the method described under formulation.

● BENZYLBENZOATE EMULSION

benzylbenzoate lotion, benzylbenzoate application.

contains: 25% benzylbenzoate in a water miscible emulsion.

● Formulation

benzylbenzoate		25	g
lanette wax		2	g
water	to	100	ml

preparation:

1. Heat 100 ml of water to the boil and allow to cool to approximately 70°C. Use this water for the preparation.
2. Melt together the benzylbenzoate and the lanette wax over gentle heat and warm to approximately 70°C.
3. Add 70 ml of the water of 70°C to this mixture and mix.
4. Stir gently until cold.
5. Add enough recently boiled and cooled water to produce 100 ml of emulsion and mix well.

packaging:

- Benzylbenzoate emulsion should be packed in well closed bottles, which prevent evaporation of water and contamination with micro-organisms, and protect the emulsion from exposure to light.
- Benzylbenzoate emulsion should be mixed until homogeneous before dispensing from stock.
- One adult patient needs 200 ml.

storage:

- Benzylbenzoate emulsion should preferably be stored below 40°C in a dark place.
- The emulsion may separate during storage. It should therefore always be shaken before dispensing or use. If carefully shaken this does not affect the quality of the emulsion.
- Benzylbenzoate emulsion should preferably be used within 3 months.
- Out of date emulsions may be less effective.
- If the package is not well closed, water may evaporate during storage. This results in an emulsion with a higher benzylbenzoate content, which may have more side effects.

● Therapy

- For external use only.
- Benzylbenzoate emulsion is used for the treatment of scabies and lice.
  For the treatment of scabies lindane cream is preferred over benzylbenzoate emulsion because it is effective after a single application. Some authors prefer benzylbenzoate emulsion for pregnant women (because lindane is thought to be teratogenic) and for children under the age of 3. For lice, non drug treatment may also be effective.

dose:

- Scabies: apply the emulsion from the neck down and repeat the application after 12 hours.
- Lice: apply the emulsion three times, at weekly intervals.

instructions for use:

- Shake the bottle before use.
- Scabies: in the evening, take a hot bath and scrub the skin to open up burrows. Apply the lotion from the neck down to the whole body and rub it into the skin. Make sure the lotion gets into contact with the whole body, including skin folds. Wash hands after application. 12 hours thereafter (the following morning) apply the emulsion a second time. 12 hours after the second and last application wash the body thoroughly with water and soap. Wash all

clothes, bedsheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water, to prevent reinfestation. It is also advisable to shake out blankets and outer wear.
Itch may persist for weeks after all the mites have been killed. Do not repeat treatment but use calamine lotion to relieve the itch.
- Lice: rub the lotion into all infected hairy areas and allow to remain for 24 hours. Wash off thorougly and comb the hair with a fine comb to remove dead lice. Wash all bedsheets, pillowcases and clothes, preferably in hot or boiling water and shake out blankets and outer wear. Repeat treatment twice at weekly intervals.

precautions:
- Scabies and lice usually affect more members of a household or community. As treating one of them is a waste of time and money, try to treat all household or community members. As to pubic lice, treat all sexual partners.
- Avoid contact of benzylbenzoate emulsion with the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of benzylbenzoate have not been reported. However, evaluate benefit/risk before using this preparation during pregnancy or lactation.

side effects:
- After frequent use contact dermatitis may develop. This is not likely to occur after three applications. Sensitization reactions are rare, irritation reactions with a burning or stinging sensation may occur. If sensitization or severe irritation reactions develop, stop the use of this preparation and do not use it again.

intoxication:
- After accidental ingestion benzylbenzoate causes central nervous system stimulation which may result in convulsions. Get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha. Convulsions may be treated with diazepam.

● Additional information

* This formula was adapted from the formula used in the British Pharmacopoeia and the Formulary of Dutch Pharmacists.

* Lanette wax may be substituted by cetomacrogol wax.

* A preservative is not needed.

* Non drug lice treatment consists of:
  - regular haircombing with a fine comb to remove lice;
  - regularly washing of clothes, bedsheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water. It is also advisable to shake out blankets and outer wear.

● CALAMINE LOTION (MODIFIED)

contains: zinc oxide 20% and phenol 0,4% in an aqueous vehicle.

● Formulation

zinc oxide	20	g
bentonite	3	g
trisodium citrate	0,5	g
glycerin	5	ml
liquefied phenol	0,5	ml
water	to 100	ml

preparation:

1. Heat 100 ml of water to the boil and allow to cool. Use this water for the preparation of the lotion.
2. Dissolve the trisodium citrate in 70 ml of the water.
3. If sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
4. Mix the zinc oxide with the bentonite.
5. Triturate this zinc oxide/bentonite mixture with the glycerin and 20 ml of the citrate solution.
6. Add the rest of the citrate solution and mix until completely homogeneous.
7. Add the liquefied phenol and mix.
8. Add enough recently boiled and cooled water to produce 100 ml and mix well.

packaging:

- Calamine lotion should be packed in well closed containers, which prevent evaporation of water and contamination with micro-organisms. Calamine lotion should be protected from exposure to light.
- Calamine lotion should be mixed until homogeneous before dispensing from stock.

storage:

- Calamine lotion should preferably be stored below 40°C.
- Calamine lotion should preferably be used within 3 months.
- Out of date calamine lotions may be less effective, and may be contaminated with micro-organisms which may cause infections.
- Calamine lotion may separate during storage. It should always be shaken before dispensing or use.

● Therapy

- For external use only.
- Calamine lotion has general soothing, cooling, antiseptic and antipruritic properties. It may be used for the treatment of itch, stinging or burning pain resulting from insect bites, allergic reactions, mild sunburn and for various other skin diseases.

dose:

- Apply the lotion several times a day, in acute disease up to a maximum of ten times a day.

instructions for use:

- Shake the lotion before use. Calamine lotion should be painted onto the skin, for example with a brush. The lotion should then be allowed to dry. It should not be covered with wrappings or bandages.

precautions:
- Calamine lotion should only be used on wounds with caution because of the risk of absorption of phenol.
- Calamine lotion should not be used on large parts of the body or for periods longer than one week unless directed to do so by a doctor. Systemic side effects may result from absorption of phenol.
- Avoid contact of calamine lotion with the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of calamine lotion have not been reported. However, evaluate benefit/risk before using this preparation during pregnancy or lactation.

side effects:
- Sensitization reactions with a burning feeling are rare but may occur. If this occurs, the use of the lotion should be stopped immediately.

intoxication:
- If calamine lotion is ingested accidentally, get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

● Additional information

* The formula given above is a modification of the calamine lotion of various pharmacopoeias, including the British Pharmacopoeia. The original formula of the British Pharmacopoeia contains 15% calamine and 5% zinc oxide instead of 20% zinc oxide. Both formulations are equivalent, but the modified formulation is much cheaper.

* Instead of bentonite, aluminium magnesium silicate (Veegum) may be used. The latter is a standardised proprietary preparation and is more expensive.

* Instead of trisodium citrate other sodium citrates may be used. This will result in a preparation in which more zinc is in solution. Such a preparation is more astringent and has a higher risk of side effects.

* Phenol itself may be used instead of liquefied phenol. To obtain the same concentration of phenol, use 0.4 grams of phenol instead of 0.5 ml of liquefied phenol. Other preservatives are less suitable. Calamine lotion without a preservative should not be stored, but it should be freshly prepared. Phenol also has a medicinal activity; calamine lotion without phenol is less effective.

● CHLORHEXIDINE DIACETATE SOLUTION 1%

contains: 1% chlorhexidine diacetate in water.

● Formulation

chlorhexidine diacetate		1 g
water	to	100 ml

preparation:

1. Heat 120 ml water to the boil and allow to cool to 30 - 40°C. Use this water for the preparation.
2. Dissolve the chlorhexidine diacetate in approximately 80 ml of this water and mix.
3. Check if all the chlorhexidine has dissolved.
4. Allow to cool completely.
5. Add enough recently boiled and cooled water to produce 100 ml and mix well.

packaging:

- Chlorhexidine diacetate solution should be packed in a well closed container. Cork closures should not be used.
- The solution should be freshly prepared, unless sterilized.

storage:

- Chlorhexidine diacetate solution should preferably be stored in a cool and dark place.
- Chlorhexidine diacetate solution 1% should preferably be used within 2 days. Sterilized solutions should preferably be used within 2 days after first opening. Unopened sterilized solutions and solutions which contain at least 7% alcohol may be kept in store. These should preferably be used within 3 months.
- Out of date chlorhexidine solutions are less effective and risk being contaminated with resistant micro-organisms. Contamination with micro-organisms is especially likely to occur after the package has been opened. These micro-organisms are likely to cause infections.

● Therapy

- For external use only.
- Chlorhexidine diacetate solution 1% is used for the disinfection of intact skin, for example prior to surgical procedures. For the disinfection of wounds, a diluted solution is preferred. Chlorhexidine is not active against bacterial spores and viruses, but iodine is. Therefore, iodine preparations are often preferred.

dose:

- Prior to surgery: apply the solution to the skin before the operation.
- Disinfection of wounds: apply a 0.1% solution to the wound once or twice daily.

instructions for use:

- Prior to surgery: the chlorhexidine solution 1% is used on intact skin. Wash the skin thoroughly and apply the solution to the skin.
- Disinfection of wounds: clean the wound carefully. Chlorhexidine is inactivated by wound debris and blood. Apply the solution to the wound. This may be done with a sterile dressing.

precautions:
- Chlorhexidine solutions 1% should not be allowed to come into contact with the eyes, because they are very irritating. If such contact has occurred accidentally, rinse immediately with a lot of water.
- Chlorhexidine can cause deafness if it comes into contact with the inner parts of the ear. For ear infections it should, therefore, only be used if the eardrum is intact. This is often difficult to assess.
- Minor wounds that heal satisfactory do not need disinfection.

pregnancy/lactation:
- Harmful effects resulting from external use of chlorhexidine solutions have not been reported.

side effects:
- Irritation and itching may develop. These may aggravate if the skin is exposed to sunlight. If sensitization or severe irritation reactions develop, stop using the preparation and do not use it again.

intoxication:
- After accidental ingestion induce vomiting with syrup of ipecacuanha.

● Additional information

* A 1% chlorhexidine solution is used for the disinfection of intact skin, a 0.1% solution is used for the disinfection of wounds. Such a 0.1% solution can be prepared by diluting a 1% solution 1 in 10 with recently boiled and cooled water. Chlorhexidine 0.1% solutions should preferably be sterilized at 121°C for 15 minutes.

* Chlorhexidine diacetate is available in the form of crystals. These have a better stability than the chlorhexidine digluconate stock solution and may be preferable. However, because chlorhexidine digluconate is widely used throughout the industrialized world, a disinfectant solution based on the digluconate has also been included in this formulary. The two solutions are interchangeable. Chlorhexidine dichloride is not soluble enough for the preparation of antiseptic solutions; it should not be used.

* Resistance against chlorhexidine is occasionally seen, especially in Pseudomonas species. Solutions should be freshly prepared to prevent growth of such resistant organisms in the solution. Alcohol (industrial methylated spirit) in a concentration of more than 7% can be used to prevent growth of these organisms in the solution. For adequate protection, add 10% industrial methylated spirit 95%, this is 10 ml of spirit for each 90 ml of chlorhexidine solution. Resistance against iodine has not been reported, this is another reason why iodine solutions are sometimes preferred.

* Unopened sterilized chlorhexidine solutions do not risk getting contaminated with micro-organisms, these can be kept in stock for some time.

● CHLORHEXIDINE DIGLUCONATE SOLUTION 1%

contains: 1% chlorhexidine digluconate in water.

● Formulation

chlorhexidine digluconate stock solution 20%	5 ml
water	to 100 ml

preparation:
1. Heat 120 ml water to the boil and allow to cool. Use this water for the preparation.
2. Mix the chlorhexidine stock solution with approximately 80 ml of this water.
3. Add enough water to produce 100 ml and mix well.

packaging:
- Chlorhexidine digluconate solution should be packed in a well closed container. Cork closures should not be used.
- The solution should be freshly prepared, unless sterilized.

storage:
- Chlorhexidine digluconate solution should preferably be stored in a cool and dark place.
- Chlorhexidine digluconate solution 1% should preferably be used within 2 days. Sterilized solutions should preferably be used within 2 days after first opening. Unopened sterilized solutions and solutions which contain at least 7% alcohol may be kept in store. These should preferably be used within 3 months.
- Out of date chlorhexidine solutions are less effective and risk being contaminated with resistant micro-organisms. Contamination with micro-organisms is especially likely to occur after the package has been opened. These micro-organisms are likely to cause infections.

● Therapy

- For external use only.
- Chlorhexidine digluconate solution 1% is used for the disinfection of intact skin, for example prior to surgical procedures. For the disinfection of wounds, a diluted solution is preferred. Chlorhexidine is not active against bacterial spores and viruses, but iodine is. Therefore, iodine preparations are often preferred.

dose:
- Prior to surgery: apply the solution to the skin before the operation.
- Disinfection of wounds: apply a 0.1% solution to the wound once or twice daily.

instructions for use:
- Prior to surgery: the chlorhexidine solution 1% is used on intact skin. Wash the skin thoroughly and apply the solution to the skin.
- Disinfection of wounds: clean the wound carefully. Chlorhexidine is inactivated by wound debris and blood. Apply the solution to the wound. This may be done with a sterile dressing.

precautions:
- Chlorhexidine solutions 1% should not be allowed to come into contact with the eyes, because they are very irritating. If such contact has occurred accidentally, rinse immediately with a lot of water.
- Chlorhexidine can cause deafness if it comes into contact with the inner parts of the ear. For ear infections it should, therefore, only be used if the eardrum is intact. This is often difficult to assess.
- Minor wounds that heal satisfactory do not need disinfection.

pregnancy/lactation:
- Harmful effects resulting from external use of chlorhexidine solutions have not been reported.

side effects:
- Irritation and itching may develop. These may aggravate if the skin is exposed to sunlight. If sensitization or severe irritation reactions develop, stop using the preparation and do not use it again.

intoxication:
- After accidental ingestion induce vomiting with syrup of ipecacuanha.

● Additional information

* A 1% chlorhexidine solution is used for the disinfection of intact skin, a 0.1% solution is used for the disinfection of wounds. Such a 0.1% solution can be prepared by diluting a 1% solution 1 in 10 with recently boiled and cooled water. Chlorhexidine 0.1% solutions should preferably be sterilized at 121°C for 15 minutes.

* Chlorhexidine diacetate is available in the form of crystals. These have a better stability than the chlorhexidine digluconate stock solution and may be preferable. However, because chlorhexidine digluconate is widely used throughout the industrialized world, a disinfectant solution based on the digluconate has also been included in this formulary. The two solutions are interchangeable. Chlorhexidine dichloride is not soluble enough for the preparation of antiseptic solutions; it should not be used.

* Resistance against chlorhexidine is occasionally seen, especially in Pseudomonas species. Solutions should be freshly prepared to prevent growth of such resistant organisms in the solution. Alcohol (industrial methylated spirit) in a concentration of more than 7% can be used to prevent growth of these organisms in the solution. For adequate protection, add 10% industrial methylated spirit 95%, this is 10 ml of spirit for each 90 ml of chlorhexidine solution. Resistance against iodine has not been reported, this is another reason why iodine solutions are sometimes preferred.

* Unopened sterilized chlorhexidine solutions do not risk getting contaminated with micro-organisms, these can be kept in stock for some time.

● DITHRANOL CREAM
anthralin cream

contains: 1% dithranol in basic cream

● Formulation

dithranol		1	g
ascorbic acid		0,5	g
lanette wax SX		15	g
liquid paraffin		12,5	g
petrolatum		22,5	g
methylparaben		0,15	g
water	to	100	g

preparation:
1. Melt together the lanette wax, the liquid paraffin and the petrolatum over gentle heat and mix.
2. Heat this mixture to about 70°C.
3. Heat sufficient water to the boil. Dissolve the methylparaben in 40 ml of this water. Allow the rest of the water to cool.
4. Allow the methylparaben solution to cool to about 70°C.
5. Add this solution to the fat mixture (2.) and mix.
6. Stir gently until cold.
7. Dissolve the ascorbic acid in 10 ml of recently boiled and cooled water.
8. Add this solution to the cream and mix until completely homogeneous.
9. Grind the dithranol carefully and triturate with approximately the same amount of cream.
10. Add the rest of the cream gradually and mix until homogeneous.
11. Add enough water that has been boiled and cooled to produce 100 grams of cream. Stir until completely homogeneous.

packaging:
- Dithranol cream should be packed in a well closed, airtight container, which prevents evaporation of water and contamination with micro-organisms, and protects the cream from exposure to light. The package should allow stirring of the cream.
  Dithranol cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, dithranol cream should be mixed until homogeneous before dispensing from stock.

storage:
- The cream should preferably be stored in a cool and dark place.
- The cream should preferably be used within 3 months.
- Degraded dithranol creams show a pink to slightly purple discolouration. Such degraded creams are less effective or ineffective.
- Out of date creams may be less effective and risk being contaminated with micro-organisms. These micro-organisms can cause infections.
- Dithranol cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not well closed, water may evaporate during storage. This results in an emulsifying ointment type preparation with a dithranol content between 1 and 2%.

● Therapy

- For external use only.
- Dithranol preparations are used for the treatment of psoriasis. Dithranol cream is a water washable preparation and therefore it is suitable for use on hairy parts of the skin. The cream is somewhat less effective than the paste, but because it is rubbed into the skin it causes less staining of clothes and bedding and less irritation on adjacent healthy skin.

dose:

- Apply once daily before going to bed.

instructions for use:

- Wash the skin carefully.
- If inhomogeneous, mix the cream before use. Apply the cream in a thin layer to the affected skin only. Rub the cream gently into the skin. Avoid contact with healthy skin. Adjacent healthy skin may be protected with petrolatum. Wash the hands after application.
- In the morning, remove the cream by washing with water only. Many soaps cause excessive staining. After all the cream has been washed away, repeat washing with water and soap.

precautions:

- Dithranol preparations are irritating to healthy skin. Avoid contact with healthy skin.
- Avoid contact of dithranol cream with the eyes.
- If intense pain or a strange skin reaction develops during the use of dithranol preparations, stop the use of such preparations.
- Dithranol preparations stain the skin, clothes and bedding, especially if alkaline soaps are used in washing.

pregnancy/lactation:

- Adverse reactions resulting from external use of dithranol during pregnancy or lactation have not been reported, but may be expected for theoretical reasons because dithranol inhibits cell division. Dithranol was also found carcinogenic in animal experiments. Consider the possible risks and the need for treatment carefully during pregnancy or lactation. Pregnancy itself may have a beneficial effect on psoriasis.

side effects:

- Dithranol preparations may produce a burning feeling. This is no reason to stop treatment. Only if intense pain develops, treatment should be stopped.
- Dithranol stains the skin, clothes and bedding.
- Dithranol cream may cause irritation reactions. These may be due to dithranol itself or to inferior qualities of white petrolatum used in the cream. Lanette wax used in the vehicle may also cause irritation.
  Sensitization due to methylparaben may develop but is rare with the concentration used in this cream. Sensitization may also develop due to the dithranol or to the yellow petrolatum used in the cream. If sensitization or severe irritation reactions develop, stop the use of this preparation and do not use it again.

● Additional information

* Lower dithranol concentrations (0.1 to 1%) may be used. Some authors recommend to start with a dithranol preparation with a low concentration, for example 0.1%. This can be raised slowly until a satisfactory response is obtained.

* Ascorbic acid is needed to prevent the rapid degradation of dithranol. If this is omitted, the cream has a maximum shelf life of 1 week. The ascorbic acid should be well mixed with the whole water phase of the cream before the dithranol is added, therefore basic cream held in stock should not be used.

* For more informa n on preparation and alternative starting materials see the monograph on basic cream.

* Dithranol can als e incorporated in either petrolatum or emulsifying ointment. In both cases it is advisa to add 2% salicylic acid to the vehicle before adding the dithranol, to prevent rapid de dation of the dithranol. These ointment preparations are more occlusive and are not reco nendable.

* Many soaps, part ularly alkaline soaps, cause excessive staining if used to wash away dithranol from th skin. Non alkaline soaps cause less staining.

● DITHRANOL PASTE
anthralin paste

contains: 1% dithranol and 2% salicylic acid in zinc paste.

● Formulation

dithranol	1	g
salicylic acid	2	g
zinc oxide	48,5	g
petrolatum	48,5	g

preparation:
1. Grind the salicylic acid. If sieves are available, sieve the salicylic acid and the zinc oxide, preferably through a 90 µm sieve.
2. Mix the salicylic acid and the zinc oxide.
3. Triturate this mixture with the petrolatum.
4. Mix until completely homogeneous.
5. Grind the dithranol carefully and triturate it with 2 grams of paste.
6. Add the rest of the paste gradually and mix until completely homogeneous.

packaging:
- Dithranol paste should be packed in a well closed airtight container, which protects the paste from exposure to light.
  A package with a wide opening is preferred as it is easier to take the paste out of such a package. Collapsible tubes are unsuitable as it can be difficult to take the paste from these tubes.

storage:
- Dithranol paste should preferably be stored in a cool and dark place.
- Dithranol paste should preferably be used within 3 months.
- Degraded dithranol paste shows a pink to purple discolouration. Out of date paste that shows no discolouration may still be used. Degraded pastes are less effective.

● Therapy
- For external use only.
- Dithranol preparations are used for the treatment of psoriasis. Dithranol paste is very difficult to wash away and hence is unsuitable for use on hairy parts of the skin.
  Dithranol cream is somewhat less effective than the paste, but because it is rubbed into the skin it causes less staining of clothes and bedding and it causes less irritation on adjacent healthy skin.

dose:
- Apply once daily before going to bed.

instructions for use:
- Wash the skin carefully.
- Apply the paste to the affected skin only. The paste layer should not be to thick. Avoid contact with healthy skin. Adjacent healthy skin can be protected with petrolatum. A loose bandage may be used to keep the paste in place. Wash the hands after application.
- In the morning, remove the paste by rinsing with some vegetable oil and washing with water and soap. Many soaps cause excessive staining.

precautions:
- Dithranol preparations are irritating to healthy skin. Avoid contact with healthy skin.
- Avoid contact of dithranol paste with the eyes.
- If intense pain or a strange skin reaction develops during the use of dithranol preparations, stop the use of such preparations.
- Dithranol preparations stain the skin, clothes and bedding, especially if alkaline soaps are used in washing.

pregnancy/lactation:
- Adverse reactions resulting from external use of dithranol during pregnancy or lactation have not been reported, but may be expected for theoretical reasons because dithranol inhibits cell division. Dithranol was also found carcinogenic in animal experiments. Consider the possible risks and the need for treatment carefully during pregnancy or lactation. Pregnancy itself may have a beneficial effect on psoriasis.

side effects:
- Dithranol preparations may produce a burning feeling. This is no reason to stop treatment. Only if intense pain develops, treatment should be stopped.
- Dithranol stains the skin, clothes and bedding.
- Dithranol paste may cause irritation reactions. These may be due to dithranol itself or to inferior qualities of white petrolatum used in the paste.
  Sensitization may develop due to dithranol or to yellow petrolatum used in the paste. If sensitization or severe irritation reactions develop, stop the use of this preparation and do not use it again.

● Additional information

* Lower dithranol concentrations (0.1 to 1%) may be used. Some authors recommend to start with a dithranol preparation with a low concentration, for example 0.1%. This can be raised slowly until a satisfactory response is obtained.

* The formula is based on the formula of zinc paste. For more information see the monograph on zinc paste.

* Salicylic acid is needed to prevent rapid degradation of dithranol. If it is omitted the paste should preferably be used within one week and should be kept cool.

* Dithranol can also be incorporated in either petrolatum or emulsifying ointment. In both cases it is advisable to add 2% salicylic acid to the vehicle before adding the dithranol, to prevent rapid degradation of the dithranol. These ointment preparations are more occlusive and are not recommendable.

* Many soaps, especially alkaline soaps, cause excessive staining if used to wash dithranol away from the skin. Non alkaline soaps cause less staining.

● EMULSIFYING OINTMENT

contains: 30% lanette wax, 25% liquid paraffin and 45% petrolatum.

● Formulation

lanette wax	30 g
liquid paraffin	25 g
petrolatum	45 g

preparation:
1. Melt all ingredients together over gentle heat.
2. Stir gently until cold.

package:
- The ointment should be packed in a container which allows stirring of the ointment. Emulsifying ointment should not be packed in collapsible tubes when the storage temperature may exceed 25°C.
- If inhomogeneous, emulsifying ointment should be mixed until homogeneous before dispensing from stock.

storage:
- Emulsifying ointment should preferably be stored below 25°C.
- Emulsifying ointment should preferably be used within 2 years.
- Out of date ointment may show a changed consistency. It may still be used as long as the consistency remains satisfactory.
- Emulsifying ointment may get inhomogeneous at a temperature of 25°C and above. Inhomogeneity does not affect the ointment, provided that it is properly mixed before dispensing or use.

● Therapy
- For external use only.
- Emulsifying ointment is a fatty ointment base used for various preparations. It is easily washed away with water and may be used on hairy parts of the skin.
- Emulsifying ointment has a mild occlusive effect and may be used as an emollient and mild moisturizer, for instance in the management of dry skin in leprosy.

dose:
- As an emollient: apply in a thin layer several times daily.

instructions for use:
- If inhomogeneous, mix the ointment before use. The ointment should be applied in a thin layer. If the ointment is used as an emollient and moisturizer, hydrate the skin by keeping it wet for 10 to 15 minutes, for example by taking a bath, before applying the ointment.

precautions:
- The ointment should be applied in a thin layer. An occlusive effect may result from thick layers of emulsifying ointment. This may cause gross hydration of the skin and subsequent complications such as secondary infections.

pregnancy/lactation:
- Harmful effects resulting from external use of emulsifying ointment have not been reported.

side effects:

- Yellow petrolatum may cause sensitization reactions. Sensitization reactions due to white petrolatum are rare. White petrolatum of inferior quality may cause irritation of the skin. Skin irritation due to lanette wax has been described. If sensitization or severe irritation reactions develop, stop the use of this preparation and do not use it again.

● Additional information

* This preparation is analogous to the emulsifying ointment of the British Pharmacopoeia.

* If no liquid paraffin is available the ointment can be prepared with petrolatum 70% and lanette wax 30%. This has only a limited effect on consistency and stability.
The reverse is not possible, an ointment prepared with 70% liquid paraffin and 30% lanette wax has poor physical stability.

* For a number of applications an alternative vehicle is petrolatum with 10% wool fat. This, however, has some drawbacks. The ointment is far more sensitizing, more occlusive, less stable, and cannot be washed away as easily as emulsifying ointment. It should not be used on hairy parts of the skin.
Petrolatum alone may be used as a vehicle but it is not water washable and very occlusive. Occlusion leads to gross hydration of the skin, which may result in secondary skin infections.

● GENTIANVIOLET SOLUTION

methylrosanilinium chloride solution, crystalviolet solution.

contains: 0.5% gentianviolet in water.

● Formulation

gentianviolet	0,5	g
water	100	ml

preparation:

1. Heat 120 ml water to the boil and allow to cool.
2. Dissolve the gentianviolet in 100 ml of this water.
3. Check for undissolved crystals on the bottom of the flask. If dissolution is incomplete, continue shaking. Gentle heat may be used.

packaging:

- Gentianviolet solution should be packed in a well closed container.
- When gentianviolet solution is dispensed from stock complete dissolution should be carefully checked by looking for undissolved crystals on the bottom. If crystals are present shake until they have completely dissolved.
- One patient needs 10 to 100 ml, this depends on localization and size of the infection. Because of the risk of bacterial contamination, the preparation should be dispensed in a one weeks supply.

storage:

- The solution should be stored at room temperature. The optimal storage temperature is 15 to 30°C. If the solution is kept below 15°C gentianviolet may crystallize from the solution.
- The solution should preferably be used within 3 months. After opening the solution is readily contaminated with micro-organisms which may cause infections. Therefore, the product should not be used for more than 1 week after first opening.
- Out of date solutions may be contaminated with resistant micro-organisms which may cause infections.
- If the package is not well closed, water may evaporate during storage. This results in a more concentrated solution which may cause more side effects.

● Therapy

- Gentianviolet solution is for external use only.
- Gentianviolet has good antimicrobial activity against Candida species. Gentianviolet solution can be used for treatment of Candida infections of skin and mouth. Candida infections of the vagina can also be treated with gentianviolet, but other pharmaceutical forms should be chosen, for instance vaginal tablets.
  Gentianviolet also has antimicrobial activity against a number of bacteria, particularly Gram positive organisms. It may therefore be used as a paintment once daily for ulcers, e.g. in leprosy. For severe or deep infections systemic antibiotics are needed.

dose:

- The solution should be applied to the affected parts of the skin or the oral mucosa once or twice daily for 3 days, or until the disease has markedly improved.

instructions for use:
- Skin infections: clean the skin with water and soap. Apply gentianviolet solution to the affected parts of the skin only. Leave the affected parts of the skin exposed to the air. Do not cover with bandages. Clean clothes and bedsheets regularly.
- Oral infections: apply the solution to the affected parts. Avoid contact with healthy parts of the mucosa. Gentianviolet solution should not be swallowed. Children should be turned face down after application to avoid swallowing.
- Ulcers: remove any necrotic tissue and callous skin around the fissure mechanically with a sterile instrument. Paint the depht of the crack with gentianviolet solution once daily. Cover with a loose bandage.

precautions:
- The solution stains clothes and bedding. It is very difficult to remove stains with water and soap. From some materials they can be removed with alcohol.
- The solution stains the skin. Staining on damaged skin may be permanent (tattooing). The solution should therefore not be used in the face.
- Undissolved gentianviolet crystals are very irritating. It is therefore important to check for complete dissolution before dispensing or use.

pregnancy/lactation:
- In animal experiments a mutagenic effect has been found. Harmful effects in humans resulting from the use of gentianviolet have been reported. Avoid the use of gentianviolet during pregnancy.

side effects:
- Irritation of the skin or mucosa may occur.
- Necrotic skin reactions are reported after the use of gentianviolet solutions of 1% or more. Such reactions will be rare with the 0.5% solution. If they develop stop using the preparation and consult a doctor.

intoxication:
- After accidental ingestion gentianviolet can damage the gullet and stomach. Get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

● Additional information

* Gentianviolet solution is often prescribed as a 1% solution. The 0.5% is as effective as the 1% solution, but less irritating and cheaper.

● HYDROCORTISONE CREAM

hydrocortisone acetate cream.

contains: 1% hydrocortisone acetate in basic cream.

● Formulation

hydrocortisone acetate	1 g
basic cream	99 g

preparation:

1. Grind the hydrocortisone acetate. If sieves are available, sieve the hydrocortisone acetate, preferably through a 90 µm sieve.
2. Triturate the hydrocortisone acetate carefully with about 1 g of basic cream until completely homogeneous.
3. Add the rest of the cream gradually and mix until completely homogeneous.

packaging:

- Hydrocortisone cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms, and protects the cream from exposure to light. The container should allow stirring of the cream. The cream should not be stored in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, hydrocortisone cream should be mixed until homogeneous before dispensing from stock.

storage:

- Hydrocortisone cream should preferably be stored in a cool and dark place. It should be kept at a temperature below 40°C, or, even better, below 30°C.
- The cream should preferably be used within 3 weeks. If the cream is exposed to temperatures higher than 40°C it should be used within 1 week.
- Out of date creams may be less effective and risk being contaminated with micro-organisms which may cause infections.
- The cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not well closed, water may evaporate during storage. This results in an emulsifying ointment type preparation with a hydrocortisone content between 1 and 2%.

● Therapy

- For external use only.
- Hydrocortisone cream has general anti-inflammatory properties. It can be used for the treatment of many skin diseases, for example eczema. Treatment is only symptomatic. Hydrocortisone cream is a water washable preparation and it is suitable for use on hairy parts of the skin. Whether a cream or an ointment is preferred depends on the local situation.

dose:

- Apply the cream up to three times daily in a thin layer.
- Do not use more than 50 grams of the cream a week, unless on doctor's instructions.

instructions for use:

- If inhomogeneous, mix the cream before use.
- Do not cover the skin with wrappings or bandages unless after doctor's instructions.

precautions:
- Do not use hydrocortisone cream on infections as they may worsen due to the cream.
- Apply hydrocortisone cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Hydrocortisone cream gives only symptomatic relieve. When treatment is stopped the disease may return.
- Hydrocortisone cream should only be used for prolonged periods on doctor's advice.
- Avoid contact of hydrocortisone cream with the eyes.
- In children growth retardation may result from the prolonged external use of corticosteroids. Regular checks on both length and weight is recommended for children during treatment with corticosteroids.

pregnancy/lactation:
- High systemic doses of corticosteroids were found to be teratogenic in animal experiments. Corticosteroids are absorbed to some extend and they may pass the placenta and influence the fetus. However, harmful effects resulting from external use of class I corticosteroids such as hydrocortisone have not been reported. Carefully evaluate the need for treatment during pregnancy.
- Corticosteroids are excreted in breast milk, but adverse effects on the baby due to external use by the mother of class I corticosteroids such as hydrocortisone have not been reported. Carefully evaluate the need for treatment during lactation.

side effects:
- Hydrocortisone cream masks infections.
- Hydrocortisone cream may delay the healing of damaged skin.
- Local side effects of corticosteroids used on the skin include irritation, an itching or burning sensation, and depigmentation. After prolonged use of corticosteroid preparations thinning of the skin may result. These effects most frequently occur in the face, on hairy parts of the skin, and in the genital region.
- Systemic side effects due to the local use of hydrocortisone cream are uncommon, but they may be very serious. They include suppression of the synthesis of corticosteroids in the adrenal glands.
- Sensitization reactions due to hydrocortisone are rare, but have been described. Methylparaben, the preservative used in the cream, may cause sensitization in rare cases. Yellow petrolatum may also cause sensitization reactions. The lanette wax used in the cream may cause irritation of the skin, but such reactions are rare. Inferior qualities of white petrolatum may also cause irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* Lower concentrations of hydrocortisone may be obtained by further dilution of the preparation with basic cream.

* If no basic cream is available, hydrocortisone ointment may be used instead. For other alternative vehicles see hydrocortisone ointment.

* If larger quantities of hydrocortisone cream are prepared with the intention to store them for some time, a freshly prepared basic cream should be used.

● HYDROCORTISONE OINTMENT

hydrocortisone acetate ointment.

contains: 1% hydrocortisone acetate in emulsifying ointment.

● Formulation

hydrocortisone acetate	1 g
emulsifying ointment	99 g

preparation:

1. Grind the hydrocortisone acetate. If sieves are available, sieve the hydrocortisone acetate, preferably through a 90 μm sieve.
2. Triturate the hydrocortisone acetate carefully with about 1 g of emulsifying ointment until completely homogeneous.
3. Add the rest of the ointment gradually and mix until completely homogeneous.

packaging:

- Hydrocortisone ointment should be packed in a well closed container protecting the ointment from exposure to light. The container should allow stirring of the ointment. Hydrocortisone ointment should not be packed in collapsible tubes when the storage temperature may exceed 25°C.
- If inhomogeneous, hydrocortisone ointment should be mixed until homogeneous before dispensing from stock.

storage:

- Hydrocortisone ointment should preferably be stored in a cool and dark place. It should be kept at a temperature below 40°C, or, even better, below 25°C.
- The ointment should preferably be used within 2 months. If the ointment is exposed to temperatures higher than 40°C it should be used within 2 weeks.
- Out of date hydrocortisone ointment may be less effective.
- Hydrocortisone ointment may get inhomogeneous at temperatures of 25°C and above. Inhomogeneity does not affect the ointment, provided that it is properly mixed before dispensing or use.

● Therapy

- For external use only.
- Hydrocortisone ointment has general anti-inflammatory properties. It can be used for the treatment of many skin diseases, for example eczema. Treatment is only symptomatic. Hydrocortisone ointment is water washable and suitable for use on hairy parts of the skin. Whether the cream or the ointment is preferred depends on the local situation.

dose:

- Apply the ointment up to three times daily in a thin layer.
- Do not use more than 50 grams of the ointment a week, unless on doctor's instructions.

instructions for use:

- If inhomogeneous mix the ointment before use.
- Do not cover with wrappings or bandages unless on doctor's instructions.

precautions:
- Do not use hydrocortisone ointment on infections as they may worsen due to the ointment.
- Apply hydrocortisone ointment in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Hydrocortisone ointment gives only symptomatic relieve. When treatment is stopped the disease may return.
- Hydrocortisone ointment should only be used for prolonged periods on doctor's advice.
- Avoid contact of hydrocortisone ointment with the eyes.
- In children growth retardation may result from the external use of corticosteroids. Regular checks on both length and weight is recommended for children during treatment with corticosteroids.

pregnancy/lactation:
- High systemic doses of corticosteroids were found to be teratogenic in animal experiments. Corticosteroids are absorbed to some extend and they may pass the placenta and influence the fetus. However, harmful effects resulting from external use of class I corticosteroids such as hydrocortisone have not been reported. Carefully evaluate the need for treatment during pregnancy.
- Corticosteroids are excreted in breast milk, but adverse effects on the baby due to external use by the mother of class I corticosteroids such as hydrocortisone have not been reported. Carefully evaluate the need for treatment during lactation.

side effects:
- Hydrocortisone ointment masks infections.
- Hydrocortisone ointment may delay the healing of damaged skin.
- Local side effects of corticosteroids used on the skin include irritation, an itching or burning sensation, and depigmentation. After prolonged use of corticosteroid preparations thinning of the skin may occur. These effects most frequently occur in the face, on hairy parts of the skin, and in the genital region.
- Systemic side effects due to the local use of hydrocortisone ointment are uncommon, but they may be very serious. They include suppression of the synthesis of corticosteroids in the adrenal glands.
- Sensitization reactions due to hydrocortisone are rare, but have been described. Sensitization reactions may also be due to yellow petrolatum. Irritation reaction to lanette wax or inferior qualities of white petrolatum may occur but are rare. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* Lower concentrations of hydrocortisone may be obtained by dilution of the preparation with emulsifying ointment.

* If no emulsifying ointment is available, petrolatum with 10% wool fat may be used. This gives a non washable preparation with a higher sensitization risk. Alternatively, petrolatum alone may be used, but this will result in a less active and more occlusive preparation.

* If larger quantities of hydrocortisone ointment are prepared with the intention to store them for some time, a freshly prepared emulsifying ointment should preferably be used.

● INDUSTRIAL METHYLATED SPIRIT 70%
alcohol 70%

contains: 70 % industrial methylated spirit in water.

● Formulation

industrial methylated spirit 95%	74 ml
water	to 100 ml

preparation:
1. Add enough recently boiled and cooled water to the spirit to produce 100 ml of solution.
2. Mix well and allow to cool.
3. Make up to exactly 100 ml with recently boiled and cooled water.

packaging:
- Industrial methylated spirit 70% should be packed in a well closed container.

storage:
- Industrial methylated spirit 70% should preferably be stored cool.
- Industrial methylated spirit 70% is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where industrial methylated spirit is stored.
- Industrial methylated spirit 70% should preferably be used within 3 months.
- Out of date industrial methylated spirit 70% may have a lower alcohol content due to evaporation of alcohol. The alcohol content can be checked by weighing exactly 100 ml of the spirit. The weight should be approximately 88.7 grams. A higher weight indicates evaporation of alcohol.

● Therapy
- For external use only.
- Industrial methylated spirit has drying, antiseptic and slightly astringent properties. It is used as a disinfectant for smooth surfaces, particularly in hospitals. For disinfection of the skin prior to surgery, iodine tincture or solution is preferred, or, alternatively, chlorhexidine solution may be used.

precautions:
- Industrial methylated spirit is highly flammable.

pregnancy/lactation:
- Harmful effects resulting from external use of industrial methylated spirit have not been reported.

side effects:
- Irritation reactions have been seen occasionally. Dermatitis may occur when less suitable qualities of industrial methylated spirit are used on the skin. If irritation or sensitization reactions develop, stop using this preparation and do not use it again.

intoxication:
- Industrial methylated spirit should only be used externally. The ocular toxicity of methanol prohibits its use in systemic preparations such as oral solutions.
- After accidental ingestion of large quantities of industrial methylated spirit get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha and bring a 5% solution of sodium bicarbonate in the stomach.

Additional information

* 70% industrial methylated spirit is a more potent disinfectant than either more concentrated or more diluted solutions. This strength should therefore be used for disinfection and antiseptic purposes.

* If 95% industrial methylated spirit is not available, but spirits with another strength are, the amount of this spirit needed can be calculated with the following formula: amount needed = 100 x strength wanted/strength available.
For strength wanted fill in 70%. For strength available fill in the strength of the industrial methylated spirit in stock.
An example: your industrial methylated spirit has a strength of 90%. You should dilute 100 x 70/90 ml = 78 ml with water to 100 ml.

● IODINE SOLUTION

iodine topical solution

contains: 2% iodine in water

● Formulation

iodine		2	g
potassium iodide		2,5	g
water	to	100	ml

preparation:

1. Iodine reacts with a great number of substances. Metallic or plastic utensils should not be used in the preparation of iodine solution. Glass and earthenware are appropriate.
2. Heat a sufficient quantity of water to the boil and allow to cool. Use this water for the preparation.
3. Dissolve the potassium iodide in 5 ml of water.
4. Dissolve the iodine in this solution.
5. Add enough recently boiled and cooled water to produce 100 ml of solution.

packaging:

- Iodine solution should be packed in well closed, airtight containers made of glass or earthenware. Metallic closures should be avoided. The container should prevent evaporation of iodine and water and it should provide protection from exposure to light.
- If iodine solution is dispensed from stock, mix the stock before dispensing.

storage:

- Iodine solution should be kept below 35°C. The solution should be protected from exposure to light.
- Iodine solution should be used within 3 months.
- During storage, evaporation of water and iodine may occur, and iodine may degrade. This will probably result in a solution with a higher iodine concentration.
- Out of date iodine solution may be less effective.

● Therapy

- For external use only.
- Iodine has a strong antiseptic activity against all micro-organisms, including bacterial spores and viruses. It is used for disinfection of intact skin and for wounds. For disinfection of intact skin, iodine tincture is preferred above iodine solution, because it has a stronger and quicker action. For wound disinfection the less irritating iodine solution is preferred, a quick action is not needed in this case.

dose:

- Disinfection of intact skin: apply the solution to the skin several minutes before the operation.
- Disinfection of wounds: apply the solution to the wound once or twice daily.

instructions for use:

- Disinfection of intact skin: wash the skin carefully and apply the solution to the skin several minutes before the operation.
- Disinfection of wounds: clean the wound carefully. Iodine is inactivated by wound debris, blood and pus. After thorough cleaning apply the solution. This may be done with a sterile dressing. Iodine treated skin should not be covered with a tight bandage.

precautions:

- Minor wounds that heal satisfactory do not need disinfection.
- Iodine treated skin should not be covered with tight or occlusive bandages, because this may result in strong irritation and blistering of the skin.
- Iodine solution is very irritating to the eyes. After accidental contact, rinse the eyes immediately with a lot of water.
- Iodine is absorbed to some extend, even through intact skin. After absorption, it interferes with the thyroid function. Iodine solution should therefore be used with great care in patients with disorders of the thyroid gland (goitre etc).

pregnancy/lactation:

- Iodine is absorbed to some extend, even through healthy, intact skin. It passes the placenta and interferes with the thyroid function of the unborn child. Iodine preparations should therefore be avoided during pregnancy, unless there is a pressing need to use them. Consider chlorhexidine as an alternative.
- Iodine is excreted in breast milk. It may interfere with the thyroid function of the newborn child. Iodine should therefore be avoided during lactation. Consider chlorhexidine as an alternative.

side effects:

- Iodine is an irritating and sensitizing substance.
- Iodine and iodides may cause acne-like skin eruptions, bullous eruptions and tumour-like lesions.
- Iodine is absorbed to some extend, even through healthy, intact skin. After chronic use on large parts of the body, this may result in a characteristic pattern of systemic side effects called iodism. Iodism is characterized by mental depression, nervousness, insomnia, sexual impotence and thyroid disfunctioning. Children are more vulnerable to iodism than adults.

intoxication:

- Iodine is corrosive and toxic when ingested. After accidental ingestion get medical advice. While waiting for a doctor, give milk and starch first and then induce vomiting with syrup of ipecacuanha. If no starch is available, sodium thiosulphate solution may be used instead.

● Additional information

* This formulation is based on iodine topical solution as included in the United States Pharmacopoeia.

* Intact skin disinfection and wound care each need a different approach. In the first case, a rapid action is needed and irritation is not a problem. But in the second case, irritation and a delay in wound healing are important, while rapid action is less so because the contact time is much longer. For intact skin disinfection iodine tincture is preferred. This is an irritating preparation, but it is very effective and has a rapid action. For wound care, the slower acting, but better tolerated, iodine solution is preferred.

* Potassium iodide is preferred over sodium iodide for this preparation because potassium iodide is already included in the WHO essential drugs list for other indications. However, sodium iodide (in the same amount) may be used as well.

* In an aqueous solution 2% iodine is generally considered effective. Higher concentrations are not needed, lower concentrations may be less effective. If alcohol is added, lower iodine concentrations are possible (refer to the monograph on iodine tincture).

● IODINE TINCTURE

iodine alcoholic solution

contains: 2% iodine in an approximately 50% alcoholic solution

● Formulation

iodine		2	g
potassium iodide		2,5	g
industrial methylated spirit 95%		50	ml
water	to	100	ml

preparation:

1. Iodine reacts with a great number of substances. Metallic or plastic utensils should not be used in the preparation of iodine solution. Glass and earthenware are appropriate.
2. Heat a sufficient quantity of water to the boil and allow to cool. Use this water for the preparation.
3. Dissolve the potassium iodide in 5 ml of water.
4. Dissolve the iodine in this solution.
5. Add the industrial methylated spirit to this solution. Iodine forms irritating substances with acetone and other ketones. The industrial methylated spirit used for the preparation of iodine tincture should be free from acetone and other ketones.
6. Add enough recently boiled and cooled water to produce 100 ml of tincture.

packaging:

- Iodine tincture should be packed in well closed, airtight containers made of glass or earthenware. Metallic closures should be avoided. The container should prevent evaporation of iodine, alcohol and water and it should provide protection from exposure to light.
- If iodine tincture is dispensed from stock, mix the stock before dispensing.

storage:

- Iodine tincture should be protected from exposure to light.
- Iodine tincture should be used within 3 months.
- During storage, evaporation of water, alcohol and iodine may occur, and iodine may degrade. This results in a tincture with a higher or lower iodine concentration.
- Out of date iodine tincture may be less effective.

● Therapy

- For external use only.
- Iodine has a strong antiseptic activity against all micro-organisms, including bacterial spores and viruses. It is used for disinfection of intact skin and for wounds. For disinfection of intact skin, iodine tincture is preferred above iodine solution, because it has a stronger and quicker action. For wound disinfection the less irritating iodine solution is preferred, a quick action is not needed in this case.

dose:

- Disinfection of intact skin: apply the tincture to the skin several minutes before the operation.
- Disinfection of wounds: apply the tincture to the wound once or twice daily.

instructions for use:

- Disinfection of intact skin: wash the skin carefully and apply the tincture to the skin several minutes before the operation.
- Disinfection of wounds: clean the wound carefully. Iodine is inactivated by wound debris, blood and pus. After thorough cleaning apply the tincture. This may be done with a sterile dressing. Iodine treated skin should not be covered with a tight bandage.

precautions:
- Minor wounds that heal satisfactory do not need disinfection.
- Iodine treated skin should not be covered with tight or occlusive bandages, because this may result in strong irritation and blistering of the skin.
- Iodine tincture is very irritating to the eyes. After accidental contact, rinse the eyes immediately with a lot of water.
- Iodine is absorbed to some extend, even through intact skin. After absorption, it interferes with the thyroid function. Iodine tincture should thus be used with great care in patients with disorders of the thyroid gland (goitre etc).
- Iodine forms irritating products with acetone and other ketones often present in industrial methylated spirit. This spirit should thus be free of such ketones. A special "acetone-free" industrial methylated spirit should be used.

pregnancy/lactation:
- Iodine is absorbed to some extend, even through healthy, intact skin. It passes the placenta and interferes with the thyroid function of the unborn child. Iodine preparations should therefore be avoided during pregnancy, unless there is a pressing need to use them. Consider chlorhexidine as an alternative.
- Iodine is excreted in breast milk. It may interfere with the thyroid function of the newborn child. Iodine should therefore be avoided during lactation. Consider chlorhexidine as an alternative.

side effects:
- Iodine is an irritating and sensitizing substance.
- Iodine and iodides may cause acne-like skin eruptions, bullous eruptions and tumour-like lesions.
- Iodine is absorbed to some extend, even through healthy, intact skin. After chronic use on large parts of the body, this may result in a characteristic pattern of systemic side effects called iodism. Iodism is characterized by mental depression, nervousness, insomnia, sexual impotence and thyroid disfunctioning. Children are more vulnerable to iodism than adults.

intoxication:
- Iodine is corrosive and toxic when ingested. After accidental ingestion, get medical advice. While waiting for a doctor, give milk and starch first and then induce vomiting with syrup of ipecacuanha. After vomiting, bring a sodium bicarbonate solution in the stomach. If no starch is available, sodium thiosulphate solution may be used instead.

● Additional information

* This formulation is based on iodine tincture as included in the United States Pharmacopoeia.

* Intact skin disinfection and wound care each need a different approach. In the first case, a rapid action is needed and irritation is not a problem. But in the second case, irritation and a delay in wound healing are important, while rapid action is less so because the contact time is much longer. For intact skin disinfection iodine tincture is preferred. This is an irritating preparation, but it is very effective and has a rapid action. For wound care, the slower acting, but better tolerated, iodine solution is preferred.

* Potassium iodide is preferred over sodium iodide for this preparation because potassium iodide is already included in the WHO essential drugs list for other indications. However, sodium iodide (in the same amount) may be used as well.

* 2% iodine in 50% spirit is effective. If the strength of the spirit is raised to 70%, the iodine concentration can be lowered to 1%. Alcohol and iodine are thus, in a certain way, interchangeable. Iodine concentrations of more than 2% are not necessary.

* If industrial methylated spirit is not available, iodine solution may be used for disinfection of intact skin, but a longer contact time is needed in this case.

● LINDANE CREAM

gammexane cream, hexachlorocyclohexane cream.

contains: 1% lindane in a water washable cream.

● Formulation

lindane		1	g
lanette wax		14	g
liquid paraffin		8	g
methylparaben		0,15	g
water	to	100	g

preparation:

1. Melt together the lanette wax and the liquid paraffin over gentle heat to approximately 70°C and mix.
2. Dissolve the lindane in this mixture.
3. Heat 75 ml of water to the boil and dissolve the methylparaben in this water. Allow the solution to cool to approximately 70°C.
4. Add the paraffin/lanette wax mixture to the solution under rapid stirring.
5. Stir gently until cold.
6. Add enough recently boiled and cooled water to produce 100 grams of cream. Stir until completely homogeneous.

packaging:

- Lindane cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms, and protects the cream from exposure to light. The package should allow stirring of the cream.
  Lindane cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, lindane cream should be mixed until homogeneous before dispensing from stock.
- One patient needs approximately 50 grams of this cream.

storage:

- The cream should preferably be stored in a dark place below 40°C.
- The cream should preferably be used within 3 months.
- Out of date creams risk being contaminated with micro-organisms which may cause infections.
- Lindane cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not well closed, water may evaporate during storage. This results in an emulsifying ointment type preparation with a lindane content between 1 and 4%. Such creams may cause toxic effects and should therefore not be used.

● Therapy

- For external use only.
- Lindane cream is used for the treatment of scabies and lice infestations. It is water washable and may be used on hairy parts of the skin. Lindane cream is preferred for the treatment of scabies, but for pregnant women and children under the age of 3 some authors prefer benzylbenzoate emulsion or sulphur cream or ointment.

dose:

- Scabies: apply the cream from the neck down to the whole body only once.
- Lice: apply the cream to the affected and adjacent parts only once.

instructions for use:

- If inhomogeneous, mix the cream before use.
- Scabies: apply the cream in a thin layer from the neck down to the whole body and rub it into the skin. Make sure the cream gets into contact with the whole body, including skin folds. Wash hands after application. Allow the cream to remain on the skin for 24 hours. Wash the body thoroughly with water and soap. Wash all clothes, bedsheets and pillowcases that have been in close contact with the skin, preferably in hot or boiling water, to prevent reinfestation. It is also advisable to shake out blankets and outer wear.
  Itch may persist for weeks after all the mites have been killed. Do not repeat treatment but use some calamine lotion to relieve the itch.
- Lice: rub the cream into all affected hairy areas and allow to remain for 24 hours. Take care to avoid all contact with the eyes. Wash off thoroughly and comb the hair with a fine comb to remove dead lice. Wash all bedsheets, pillowcases and clothes, preferably in hot or boiling water and shake out blankets and outer wear.

precautions:

- Lindane is a toxic substance. Misuse may result in serious intoxications. When using lindane follow these rules:
- Do not wash the skin or take a bath immediately before application;
- Do not repeat lindane treatment within one month or more than twice a year.
- Lindane cream can be more toxic for malnourished people and small children under the age of 3. Benzylbenzoate emulsion or sulphur ointment may be used instead, but they are less effective.
- Avoid contact with the eyes.
- Lindane cream should not be used by people who have had allergic skin reactions to lindane cream or basic cream.
- Scabies and lice usually affect more members of a household or community. As treating one of them is a waste of time and money, try to treat all household or community members. As to pubic lice, treat all sexual partners.

pregnancy/lactation:

- In animal experiments a mutagenic effect of lindane has been shown. Lindane is absorbed to some extend after topical application. Therefore, a toxic effect to the unborn child can be expected, but the clinical relevance of this toxicity is still under discussion. Carefully evaluate the need for treatment before using lindane cream during pregnancy, or consider the use of benzylbenzoate as an alternative.
- Small amounts of lindane are excreted in breast milk. The clinical effect of this is probably insignificant. However, evaluate the need for treatment during lactation carefully.

side effects:

- Sensitization due to methylparaben may occur but it is unlikely with the concentration used in this cream.
  Irritation due to lanette wax has been described, but is rare.
  Irritation or sensitization reactions to lindane are very uncommon after single use. Contact dermatitis may result from repeated use. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

intoxication

- Lindane has a general toxic effect on the nervous system. After prolonged extensive use of the cream restlessness, muscle spasms and seizures may occur. Coma and death from respiratory failure may occur. It is important not to overuse lindane cream.
- After ingestion gastric lavage is only of value if undertaken rapidly. Diazepam can be given intravenously to treat seizures. Otherwise treatment is supportive, it consists of keeping the patient warm, assisting respiration etc.

Additional information

* This formula has been modified from the formula of the British Pharmacopoeia for lindane cream first published in the addendum 1977. A preservative is added. If this is omitted, the cream should not be held in store.

* The cream can be prepared with other lindane concentrations as well. For the treatment of lice a 0.4% or even a 0.1% cream is often used. To prepare such creams use 0.4 g or 0.1 g instead of 1 g of lindane for 100 g of cream.

* In the preparation of lindane cream, the oil phase is added to the water phase under rapid stirring. This differs from the usual preparation method for creams. The reason for the use of this method for the preparation of lindane cream is that it ensures a small droplet size and a homogeneous distribution of droplets.

* Non drug lice treatment consists of:
  - regular haircombing with a fine comb to remove lice;
  - regular washing of clothes, bedsheets and pillowcases that has been in close contact with the skin, preferably in hot or boiling water. It is also advisable to shake out blankets and outer wear.

* In industrialized countries in North America and Europe the scabies mite is occasionally found to be resistant to lindane. Treatment failure, however, is difficult to assess, because the itch persists for some time after all the mites have been killed. In case of a treatment failure, try benzylbenzoate emulsion. Avoid more than 2 lindane treatments per year.

* Lice may be resistant too. Try intensive non drug treatment for resistant lice.

* Lindane has been used in various ointments, such a petrolatum, petrolatum with wool fat, vegetable oils and emulsifying ointment. These vehicles have some occlusive and hydrating effect which can cause more lindane absorption and higher toxicity. In addition, these vehicles are not so easily washed away as the cream. This can cause more absorption because the product remains on the skin for a longer period. This affects the safety of the preparation. Therefore we strongly recommend to stick to the generally used vehicles such as this cream. Lindane cattle dip has also been used for humans. The risks of this kind of preparation are unknown.

● MICONAZOLE CREAM

contains: 2% miconazole nitrate in a water washable cream.

● Formulation

Commercial preparation. Miconazole cream is marketed under various trade names.

packaging:
- See product specifications.

storage:
- See product specifications.
- Out of date creams may be less effective and may be contaminated with micro-organisms which may cause infections.
- Miconazole cream may get inhomogeneous at higher temperatures. If this happens, the cream should be mixed before dispensing or use.
- If the package is not well closed, water may evaporate during storage. This results in a preparation with different characteristics.

● Therapy

- For external use only.
- Miconazole cream is a broad spectrum antimycotic preparation. It can be used for all superficial skin mycoses, including candidiasis. Miconazole cream is water washable and may be used on hairy parts of the skin. Miconazole cream is relatively expensive. For the treatment of superficial mycotic skin infections Whitfield's cream or ointment is preferred. For the treatment of superficial candidiasis gentianviolet solution is preferred. For pityriasis versicolor sodium thiosulphate is the drug of first choice. If these are ineffective or not well tolerated, miconazole cream is a good alternative.

dose:
- See product specifications.
- Apply twice daily until the lesions are completely cleared, usually 2 to 5 weeks.

instructions for use:
- See product specifications.
- Clean the skin with water and soap before application of the cream. Apply the cream in a thin layer to prevent occlusion. Occlusion resulting from thick layers of cream may lead to an exacerbation of the infection. Do not cover with wrappings or bandages.

precautions:
- See product specifications.
- Avoid contact of miconazole cream with the eyes.
- Occlusion and hydration favour growth of Candida species.

pregnancy/lactation:
- See product specifications.
- Harmful effects resulting from external use of miconazole cream have not been reported.

side effects:
- Irritation reactions with a burning feeling may develop.
- Sensitization reactions are rare. If any strange skin reaction occurs, the use of the cream should be stopped.

● NYSTATIN PREPARATION

contains: 100.000 units nystatin per gram in a cream or ointment.

● Formulation

Commercial preparation. Nystatin is marketed in various preparations and under various trade names. Both creams or ointments may be used, but creams are preferred.

packaging:
- See product specifications.

storage:
- See product specifications.
- Nystatin preparations should be stored in a refrigerator.
- Out of date nystatin preparations, or nystatin preparations that have not been stored in a refrigerator, may be less effective or ineffective, and may be contaminated with micro-organisms which may cause infections.
- Nystatin preparations may get inhomogeneous at higher temperatures. If inhomogeneous, they should be mixed before dispensing or use. If nystatin preparations are exposed to temperatures high enough to cause inhomogeneity, the nystatin is most likely to be degraded and the preparation is unreliable. Such preparations should be discarded.

● Therapy

- For external use only.
- Nystatin has a strong fungistatic activity against Candida species. Nystatin is an instable drug. It is unsuitable for general use in tropical countries. Candidiasis should preferably be treated with gentianviolet solution. The next choice is miconazole cream. Nystatin may be useful for well equipped hospitals that are able to store drugs in a well functioning refrigerator. The cream is preferable to the ointment because it is less occlusive. Occlusion and hydration create a favourable environment for the growth of Candida species and various bacteria.

dose:
- See product specifications.
- Apply the nystatin preparation twice daily for 2 weeks.

instructions for use:
- See product specifications.
- Wash the skin carefully with water and soap and allow to dry. Apply the cream or ointment in a thin layer to prevent occlusion.
  Do not cover with wrappings or bandages.

precautions:
- See product specifications.
- Avoid contact of nystatin preparations with the eyes.
- Symptomatic relief usually occurs 1 to 3 days after starting the medication. Treatment should be continued for 2 weeks to prevent recurrences.

pregnancy/lactation:
- See product specifications.
- Harmful effects resulting from external use of nystatin preparations have not been reported.

side effects:
- See product specifications.
- Irritation and sensitization are reported but are rare. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● PARA AMINOBENZOIC ACID CREAM

PABA cream

contains: 5% para aminobenzoic acid in basic cream.

● Formulation

para aminobenzoic acid	5 g
basic cream	95 g

preparation:

1. Para aminobenzoic acid containing preparations are not legally allowed in some countries. Check this before preparing or dispensing para aminobenzoic acid preparations.
2. Grind the para aminobenzoic acid. If sieves are available, sieve the para aminobenzoic acid, preferably through a 90 µm sieve.
3. Triturate the para aminobenzoic acid with approximately 10 grams of the cream.
4. Add the rest of the cream gradually and mix until completely homogeneous.

packaging:

- Para aminobenzoic acid cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms and protects the cream from exposure to light.
  The package should allow stirring of the cream.
  Para aminobenzoic acid cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, para aminobenzoic acid cream should be mixed until homogeneous before dispensing from stock.

storage:

- The cream should preferably be stored in a dark place below 40°C.
- The cream should preferably be used within 3 months.
- Out of date creams may be less effective and risk being contaminated with micro-organisms which may cause infections. Degraded creams show a strong discolouration. The stronger the colour of the preparation, the more degradation has occurred. A slight discolouration is not an indication for gross degradation. Slightly discoloured preparations may still be used.
- The cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not closed well, water may evaporate during storage. This results in an emulsifying ointment type preparation with a para aminobenzoic acid content between 5 and 10%. This does not necessarily impair the effectiveness of the cream, but sensitization risks may be higher.

● Therapy

- For external use only.
- Para aminobenzoic acid cream is used as a sunscreen. It absorbs part of the ultraviolet rays, particularly those responsible for sunburn (UV-B). Para aminobenzoic acid gives only partial protection against UV-A ultraviolet rays which may cause phototoxic reactions and reactions in diseases like lupus erythematoidus etc. The solution is more effective than the cream. The cream vehicle is easily washed away with water. For full protection a sun blocker like zinc paste can be used, but this is a messy preparation.

dose:

- Apply the cream in a thin layer every 2 hours and immediately after swimming or bathing.

instructions for use:
- Full benefit of the cream is obtained if it is applied at least one hour before the first exposure to sunlight.
- The cream should be applied in a thin layer to prevent occlusion. With extensive sweating occlusion may, occasionally, result in infections.
- If inhomogeneous, mix the cream before use.
- The cream discolours slightly on standing, this does not affect its activity.

precautions:
- Do not use para aminobenzoic acid cream on people allergic to para aminobenzoic acid or related compounds (local anesthetics), or to basic cream or one of its constituents.
- Para aminobenzoic acid cream stains skin and clothes.
- Avoid contact of para aminobenzoic acid cream with the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of para aminobenzoic acid containing preparations have not been reported, but may be expected for theoretical reasons. Carefully evaluate the need for treatment during pregnancy.

side effects:
- Sensitization or photosensitization reactions due to para aminobenzoic acid have been reported after the use of para aminobenzoic acid containing preparations, but considering the massive use of para aminobenzoic acid over the years, they are rare.
- Sensitization due to methylparaben may occur, but is rare with the concentration used in this cream. Sensitization due to yellow petrolatum may occur, but is rare.
  Irritation due to lanette wax has been described. Inferior qualities of white petrolatum may also cause irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* If large amounts of this cream are prepared with the intention to store them for some time, a freshly prepared basic cream should be used.

* When preparing para aminobenzoic acid cream the double amount of basic cream should be used to triturate the para aminobenzoic acid, instead of the usual equal amounts. This is for reasons of stability of the resulting cream.

* If no basic cream is available, emulsifying ointment may be used.

● PARA AMINOBENZOIC ACID SOLUTION

PABA solution, para aminobenzoic acid lotion

contains: 5% para aminobenzoic acid in an alcoholic solution.

● Formulation

para aminobenzoic acid	5	g
glycerin	20	ml
industrial methylated spirit 95%	60	ml
water	to 100	ml

preparation:

1. Para aminobenzoic acid containing preparations are not legally allowed in some countries. Check this before preparing or dispensing para aminobenzoic acid preparations.
2. Heat 60 ml of water to the boil and allow to cool. Use this water for the preparation.
3. Dissolve the para aminobenzoic acid in the industrial methylated spirit.
4. Add the glycerin to this solution.
5. Make up to 100 ml with recently boiled and cooled water, mix well and allow to cool.
6. Check the volume and, if necessary, make up again to 100 ml with recently boiled and cooled water.

packaging:

- Para aminobenzoic acid solution should be packed in a well closed container, which protects the solution from exposure to light.

storage:

- Para aminobenzoic acid solution should preferably be stored in a cool and dark place.
- Para aminobenzoic acid solution is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where para aminobenzoic acid solution is stored.
- Para aminobenzoic acid solution should preferably be used within 3 months.
- Out of date para aminobenzoic acid solution may have a lower alcohol content due to evaporation of alcohol. This will result in a higher para aminobenzoic acid content but not necessarily in a more active preparation. If much alcohol is evaporated, the solution should be discarded.
  Due to degradation of para aminobenzoic acid out of date solutions may be less effective. Degraded solutions show a marked discolouration. The stronger the colour of the solution, the more degradation has occured. A slight discolouration is not an indication for gross degradation and the solution may still be used.

● Therapy

- For external use only.
- Para aminobenzoic acid solution is used as a sunscreen. It absorbs part of the ultraviolet rays, particularly those responsible for sunburn (UV-B). Para aminobenzoic acid gives only partial protection against UV-A ultraviolet rays which may cause phototoxic reactions and reactions in diseases like lupus erythematoidus etc. The solution is more effective and less occlusive than the cream, but also less economic. For full protection a sun blocker like zinc paste can be used, but this is a messy preparation.

dose:

Apply the solution every 2 hours and immediately after swimming or bathing, and allow to dry.

instructions for use:
- Full benefit of the solution is obtained if it is applied at least one hour before the first exposure to sunlight.
- The solution discolours slightly on standing, this does not affect its activity.

precautions:
- Para aminobenzoic acid solution is highly flammable.
- Do not use para aminobenzoic acid solution on people that are allergic to para aminobenzoic acid or related compounds (local anesthetics).
- Avoid contact of para aminobenzoic acid solution with the eyes.
- Para aminobenzoic acid solution stains the skin and clothes.

pregnancy/lactation:
- Harmful effects resulting from external use of para aminobenzoic acid containing preparations have not been reported, but may be expected for theoretical reasons. Carefully evaluate the need for treatment during pregnancy.

side effects:
- Irritation reactions are seen occasionally. Dermatitis may result from the use of unsuitable qualities of industrial methylated spirit.
  Sensitization or photosensitization reactions due to para aminobenzoic acid have been reported after the use of para aminobenzoic acid containing preparations, but considering the massive use of para aminobenzoic acid over the years, they are rare. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

intoxication:
- After accidental ingestion of large quantities of para aminobenzoic acid solution get medical advice. While waiting for a doctor induce vomiting with syrup of ipecacuanha and bring a 5% sodium bicarbonate solution in the stomach.

● Additional information

* The preparation contains glycerin to minimize the drying properties of the preparation. This adds to the protective effect of the solution. It may be left out.

● PETROLATUM

vaseline, soft paraffin

● Formulation

packaging:
- Petrolatum should be packed in a container that allows mixing of the petrolatum.
- If inhomogeneous, petrolatum should be mixed until homogeneous before dispensing from stock.

storage:
- Petrolatum does not require special storage conditions.
- At temperatures of 30°C and above bleeding or partial melting can cause inhomogeneity. Inhomogeneity does not affect the preparation, provided that it is properly mixed before dispensing or use.
- Petrolatum should preferably be used within 2 years.
- There are no major risks involved in the use of out of date petrolatum.

● Therapy

- For external use only.
- Petrolatum has good protective properties and a strong occlusive effect. It may be used as a protective or as a moisturizing preparation. It is particularly useful for the management of dry skin in leprosy patients. Petrolatum is very difficult to remove from the skin. It should therefore not be used on hairy parts of the skin.
- Petrolatum is used as a vehicle for certain drugs, such as salicylic acid.

dose:
- Apply petrolatum regularly to the skin.

instructions for use:
- If used as a protective, apply petrolatum in a layer just thick enough to provide adequate protection.
- If used as a moisturizer, hydrate the skin first by keeping it wet for 10 to 15 minutes. This can be done by taking a bath. Dry the skin surface and apply petrolatum in a thin layer.
- To remove petrolatum from the skin rinse with some vegetable oil first.

precautions:
- Do not use petrolatum in hot and/or humid climates unless hydration of the skin is especially wanted.

pregnancy/lactation:
- Harmful effects due to external use of petrolatum have not been reported.

side effects:
- Gross hydration due to the occlusive effect of petrolatum can cause complications such as secondary infections.
- Sensitization reactions have been described due to constituents of yellow petrolatum. Sensitization due to white petrolatum is rare. Inferior qualities of white petrolatum however may cause irritation of the skin. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* For the management of dry skin, especially for leprosy patients, local vegetable oils or emulsifying ointment may be used instead of petrolatum.

● POTASSIUM PERMANGANATE
stock solution for dilution

contains: 1% potassium permanganate in water.

● Formulation

potassium permanganate	1 g
water	100 ml

preparation:
1. Heat 120 ml of water to the boil and allow to cool. Use this water for the preparation.
2. Dissolve the potassium permanganate in 100 ml of this water.
3. Make sure that the dissolution is complete, preferably by filtering the solution. Filtering should not be done over a filter made from organic or metallic materials. Glass filters are suitable.

packaging:
- The solution should be packed in a dark coloured, well closed glass bottle.
- Bottles should bear the warning: "Do not use undiluted".
- The amount needed per patient depends on the instructions for use. Relatively small amounts are needed because the stock solution has to be diluted before use.

storage:
- The solution should preferably be stored in a cool and dark place.
- The solution should be used within one month.
- Degraded solutions show a brown colour instead of the normal dark purple. Degradation is easily observed in diluted solutions, these should not be brownish, but pink.
- Degraded solutions are less effective or even ineffective, and more staining may occur with degraded solutions.

● Therapy
- For external use only. Should be diluted before use.
- Potassium permanganate solution has a strong antiseptic action and astringent properties, but it is rapidly inactivated after application. It may be applied to the skin or it may be used in the bath water. For the treatment of minor skin infections in leprosy soakings with diluted potassium permanganate solution twice daily during 10-15 minutes can be used.

dose:
- Apply once or twice daily, dilute before use.

instructions for use:
- The solution should be freshly diluted before each use. The stock solution should be diluted with boiled and cooled water until a pink colour is obtained. The right colour has been described as "blotting paper pink" or "as pink as a fingernail". Approximately the right dilution is obtained if a teaspoon full of stock solution is added to about 300 ml of water. In many countries this is approximately the content of a Coca Cola bottle. The solution resembles soft drinks but it is toxic. Therefore the diluted solution should not be mixed or kept in such a Coca Cola bottle.
- Wash the skin with water and soap and dry.
  Wet the skin frequently with the diluted solution during 10 minutes. Potassium permanganate solution is rapidly inactivated so it should be reapplied often during this 10 minutes treatment time.
  Rinse the skin thoroughly with water and dry.
  Discard the rest of the diluted solution.

- Potassium permanganate can be used for antiseptic baths in the same diluted concentration.
- Stains can be removed from skin and bedding or textiles with a diluted sodium thiosulphate solution.

precautions:
- Potassium permanganate crystals and strong solutions are very irritating and can cause severe chemical burns. Potassium permanganate dissolves very slowly in water. Therefore crystals should never be dispensed to patients. In some countries tablets for dissolution are marketed. Such tablets should not be given to patients as they may take them orally.
- Dilute before use.
- Potassium permanganate tablets and strong solutions are used vaginally in some regions for their supposed abortive effects. Such use results in serious damage to the vaginal wall, corrosive burns, and peritonitis. Vascular collapse may result.
- Stains on the skin may occasionally be permanent, especially if the solution is used for prolonged periods of time.

pregnancy/lactation:
- Harmful effects resulting from external use of potassium permanganate solutions have not been reported.

side effects:
- Potassium permanganate solutions stain the skin and all textiles that come into contact with it. Staining of the skin may be permanent after prolonged use of the solution.

intoxication:
- Potassium permanganate stock solution is irritating. Strong solutions and crystals are irritating and may cause severe chemical burns. After contact with skin or eyes rinse immediately with a lot of water.
- Ingestion causes nausea and vomiting. Liver and kidneys may get damaged, as well as the cardiovascular system. The fatal dose is assumed to be approximately 10 grams for adults. Death may occur within one month after intoxication. After accidental ingestion give milk immediately to reduce absorption. Get medical advice. Otherwise treatment is supportive and consists of keeping the patient warm, assisting respiration, etc.

● Additional information

* Some authors recommend dispensing potassium permanganate crystals to be dissolved at home. This is inadmissible. Potassium permanganate dissolves very slowly and ulcerations and chemical burns may result from very small undissolved crystals. For the same reason, tablets are unsuitable.

* The solution is rapidly inactivated by organic matter. Degradation is very much increased by the degradation products of potassium permanganate. If the stock solution is filtered over organic or metallic filters, for example over paper filters or cottonwool, it will contain degradation products. As a result of this, it will not be stable.
The solution is rapidly inactivated by the human skin. Therefore, it should be reapplied frequently during 10 minutes.

● SALICYLIC ACID OINTMENT

contains: 5% salicylic acid in petrolatum

● Formulation

salicylic acid	5 g
petrolatum	95 g

preparation:

1. Grind the salicylic acid. If sieves are available, sieve the salicylic acid, preferably through a 90 µm sieve.
2. Triturate the salicylic acid with an equal amount of petrolatum.
3. Add the rest of the petrolatum gradually and mix until completely homogeneous.

packaging:

- Salicylic acid ointment should be packed in a container, which allows stirring of the ointment.
- Salicylic acid ointment should not be packed in collapsible tubes when the storage temperature may exceed 25°C.
- If inhomogeneous, salicylic acid ointment should be mixed until homogeneous before dispensing from stock.

storage:

- Salicylic acid ointment should preferably be stored below 25°C.
- The ointment should preferably be used within 2 years.
- Out of date ointment may be less effective and more irritating.
- Salicylic acid ointment may get inhomogeneous at temperatures of 30°C and above. Inhomogeneity does not affect the ointment, provided that it is properly mixed before dispensing or use.

● Therapy

- For external use only.
- Salicylic acid ointment has keratolytic and hydrating properties. It is used for the treatment of hyperkeratotic conditions such as corns and calluses and for psoriasis. Acne is best treated with a drying preparation, such as salicylic acid solution. This ointment should not be used for acne.
  Salicylic acid ointment is not easily washed away from the skin and should not be used on hairy parts of the skin.

dose:

- Apply the ointment once or twice daily.

instructions for use:

- Wash the skin before application of the ointment.
- Apply the ointment in a thin layer to prevent excessive hydration of the skin.
- The ointment is difficult to remove from the skin. It may be useful to rinse the skin with a vegetable oil first.

precautions:

- Salicylic acid ointment should not be used for longer periods on large parts of the body, as this may lead to systemic intoxication.
- Small children should not receive salicylic acid ointment for long periods.

pregnancy/lactation:

- Teratogenic effects after the use of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans due to external use of salicylic acid have not been described. Evaluate benefit/risk before using salicylic acid during pregnancy.
- After external use of salicylic acid containing preparations by the mother, salicylic acid is excreted in the breast milk. However, no adverse effects on the child have been reported after external use of salicylic acid by the mother. Evaluate benefit/risk before using salicylic acid during lactation.

side effects:

- Sensitization reactions due to constituents of yellow petrolatum have been described. Sensitization due to white petrolatum is rare. Sensitization to salicylic acid may develop in rare cases after long term treatment.
  Inferior qualities of white petrolatum may cause irritation. Salicylic acid itself may also cause irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.
- Salicylic acid inhibits blood coagulation. This effect is not likely to be a practical problem after external use of salicylic acid. People with blood coagulation problems (e.g. users of anti-coagulants) should only use salicylic acid containing preparations under close medical supervision.

intoxication:

- Excessive or long term use of salicylic acid containing preparations may cause systemic intoxication. This is not likely to occur after the use of salicylic acid containing preparations on the skin, with the exception of long term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Such systemic intoxication is characterised by:
- slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
- more severe intoxication: excitation, confusion, fever and convulsions.
- severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.
  If such effects occur, the use of the preparation should be stopped immediately.

● Additional information

* Other concentrations of salicylic acid ranging from 2 to 6% may be used.

● SALICYLIC ACID SOLUTION

contains: 5% salicylic acid in an alcoholic solution.

● Formulation

salicylic acid	5 g
industrial methylated spirit 70%	100 ml

preparation:

1. Dissolve the salicylic acid in the industrial methylated spirit.

packaging:

- Salicylic acid solution should be packed in a well closed container.
- One patient needs 100 ml for a four weeks' treatment.

storage:

- Salicylic acid solution should preferably be stored in a cool place.
- Salicylic acid solution is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where salicylic acid solution is stored.
- Salicylic acid solution should preferably be used within 3 months.
- Out of date salicylic acid solution may have a lower alcohol content due to evaporation of alcohol. This will result in a higher salicylic acid content. If much alcohol is evaporated, the solution should be discarded.

● Therapy

- For external use only.
- Salicylic acid solution is used in the treatment of acne. It has keratolytic and drying properties. It is preferred to sulphur lotion, which can also be used in acne.

dose:

- Apply the solution twice daily. Therapy must generally be continued for several months.

instructions for use:

- Wash the skin with water and soap and dry. Apply the solution with some cottonwool or a clean piece of cloth, allow to dry.

precautions:

- Salicylic acid solution should not be used for extended periods of time on large parts of the body, as this may lead to systemic intoxication. The use on small parts of the body in acne is considered safe.
- Small children should not receive salicylic acid solution for long periods at all.

pregnancy/lactation:

- Teratogenic effects after the use of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans due to external use of salicylic acid have not been described. Evaluate benefit/risk before using salicylic acid during pregnancy.
- After external use of salicylic acid containing preparations by the mother, salicylic acid is excreted in the breast milk. However, no adverse effects on the child have been reported after external use of salicylic acid by the mother. Evaluate benefit/risk before using salicylic acid during lactation.

side effects:
- Local irritation may occur, but has rarely been reported. If irritation or sensitization reactions develop, stop using this preparation and do not use it again.
- Salicylic acid inhibits blood coagulation. This effect is not likely to be a practical problem after external use of salicylic acid. People with blood coagulation problems (e.g. users of anti-coagulants) should only use salicylic acid containing preparations under close medical supervision.

intoxication:
- Excessive or long term use of salicylic acid containing preparations may cause systemic intoxication. This is not likely to occur after the use of salicylic acid containing preparations on the skin, with the exception of long term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Such systemic intoxication is characterised by:
- slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
- more severe intoxication: excitation, confusion, fever and convulsions.
- severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.
  If such effects occur, the use of the preparation should be stopped immediately.
- Accidental ingestion of salicylic acid solution produces a complex clinical picture, because at least three important toxic substances are involved: salicylic acid, alcohol and methanol. After accidental ingestion get medical advice. While waiting for a doctor induce vomiting with syrup of ipecacuanha and bring a 5% sodium bicarbonate solution in the stomach.

● Additional information

* Lower concentrations of salicylic acid, for example 2%, may be used.

SILVER NITRATE SOLUTION

contains: 0.5% silver nitrate in water.

Formulation

silver nitrate	0,5	g
water	100	ml

preparation:
1. Heat 120 ml of water to the boil and allow to cool. Use this water for the preparation.
2. Avoid contact of the silver nitrate with metallic or organic materials. Use glass or earthenware.
3. Dissolve the silver nitrate in 100 ml of water.

packaging:
- Silver nitrate solution should be packed in a well closed, dark coloured glass bottle. This bottle should not have a metallic cap. Metallic containers should not be used.

storage:
- The solution should preferably be stored in a cool and dark place.
- The solution should be used within one week.
- Degraded solutions show a dark discolouration. These solutions are less active and may be contaminated with micro-organisms which may cause infections. Degraded solutions can better be avoided.

Therapy
- For external use only.
- Silver nitrate solution has a strong antiseptic action. It also has some astringent properties. Silver nitrate solution is used to prevent infection of large deep burns. For primary health care, this solution is preferred to silversulphadiazine cream for reasons of stability. Silver nitrate solution may also be used for leg ulcers.

instructions for use:
- Burns: silver nitrate treatment should be started immediately after burning, or at least within a few hours. After cleaning the wound and removal of necrotic and loose tissue the wound should be covered with several layers of sterile, course mesh gauze. These dressings can be secured with circular bandages and they should be saturated with silver nitrate solution every two hours. The dressings may be covered with light cotton covers to prevent excessive evaporation. The dressings should be kept saturated at all times. Dressings should be changed once daily.
- Ulcers: leg ulcers infected with Pseudomonas may be treated with silver nitrate compresses. These should be changed every hour.

precautions:
- Silver nitrate solution prevents infection but it is unable to sterilize the wound. Treatment should, therefore, be started immediately after burning, or at least within a few hours. Afterwards, treatment becomes rapidly less effective as the wound will already be infected with micro-organisms.
- The solution changes the wound appearance and delays rejection of necrotic tissue. This dictates very careful wound management.
- Silver nitrate solutions of 1% or more may cause skin necrosis.
- The use of silver nitrate solution on large burns may cause hypochloriaemia.
- The use of silver nitrate solution on burns infected with nitrate-reducing micro organisms may cause methaemoglobinaemia.

pregnancy/lactation:
- Harmful effects resulting from external use of silver nitrate solutions have not been reported.

side effects:
- The solution causes staining of wounds and skin. Staining may be permanent. Silver nitrate solutions also stain clothes and bedding.
- Long term use of silver nitrate solution may cause argyria, which is a slate-blue, irreversible discolouration of the skin.
- Silver nitrate solution may cause skin irritation.

intoxication:
- After accidental ingestion of silver nitrate solution get medical advice. While waiting for a doctor give a 1% sodium chloride solution (household salt) in water several times. Empty the stomach and give sodium sulphate as a purgative. If analgesics are needed to treat the pain, paracetamol is preferred over aspirin.
- After contact with skin or eyes rinse with a lot of water immediately. Sodium thiosulphate solution may be used to treat chemical burns due to silver nitrate.

● Additional information

* Stains may be removed with an aqueous solution containing 8% thiourea and 8% citric acid.

* If the water used for the preparation of silver nitrate solution contains much chlorides, a silver chloride precipitate will be formed. If such problems arise, use distilled water for the preparation of the solution.

● SILVERSULPHADIAZINE CREAM

contains: 1% silversulphadiazine in a water washable cream.

● Formulation

Commercial preparation. Silversulphadiazine is marketed under various trade names.

packaging:
- See product specifications.
- The cream is sterile, it should not be repacked.

storage:
- See product specifications.
- The cream should be stored at a temperature below 25°C.
- After first opening the cream is readily contaminated with micro-organisms which may cause infections. Therefore, the product should not be used longer than 7 days after first opening.
- Degraded creams show a slight greyish discolouration. They are less effective.
- The cream may get inhomogeneous at higher temperatures. Mixing the cream is not recommended as this is likely to result in microbial contamination. Exposure to temperatures higher than 25°C should therefore be avoided.

● Therapy

- For external use only.
- Silversulphadiazine cream is applied to deep extensive burns to prevent infection. In primary health care silver nitrate solution is preferred for reasons of stability. Silversulphadiazine cream may be used in specialised hospitals.

dose:
- See product specifications.
- The cream should be applied at least once daily to the wound.

instructions for use:
- See product specifications.
- The cream should be applied to the wound in a layer of 2 - 3 millimeters. This can be done directly or on a sterile gauze. A clean spatula may be used to apply the cream.
- To wash away the cream, use a sterile isotonic sodium chloride solution.

precautions:
- See product specifications.
- The cream prevents infection but is unable to sterilize the wound. Treatment should, therefore, be started immediately after burning, or at least within a few hours. Afterwards, treatment becomes rapidly less effective as the wound will already be infected with micro-organisms.
- The cream changes the wound appearance and delays rejection of necrotic tissue. This dictates very careful wound management.

pregnancy/lactation:
- Harmful effects resulting from external use of silversulphadiazine cream have not been reported, but systemic sulfa preparations are suspected. Evaluate benefit/risk before using this cream during pregnancy.
- Whether the use of oral sulfa preparations by the mother during lactation constitutes a risk for the infant is still a matter of discussion, but the risk is low. The risk of externally used sulfa preparations is most probably insignificant.

side effects:
- See product specifications.
- Pain and a burning feeling may occur.

● SODIUM THIOSULPHATE

contains: sodium thiosulphate. After dissolution 10% sodium thiosulphate in water.

● Formulation

sodium thiosulphate	30 g

packaging:
- Sodium thiosulphate crystals should be packed in 30 grams packages. Packaging materials should protect the crystals from humidity.
- Sodium thiosulphate crystals should be dissolved in water at home.
- One patient needs 30 grams.

storage:
- Sodium thiosulphate should preferably be stored in a cool and dry place.
- Sodium thiosulphate should preferably be used within 2 years.
- Out of date sodium thiosulphate may be less effective.
- Ready for use sodium thiosulphate solution should preferably be used within a week.

● Therapy
- For external use only.
- Sodium thiosulphate is used for the treatment of pityriasis versicolor. This disease can also be treated with miconazole cream, but this is much more expensive.

dose:
- Apply the solution twice daily to the affected parts of the skin.

instructions for use:
- Dissolve the crystals in approximately 300 ml of clean water of potable quality. In many countries this is approximately the content of a Coca Cola bottle. The solution should preferably not be mixed or kept in a Coca Cola bottle, because it resembles softdrinks. If a Coca Cola or other soft drink bottle is used for the dissolution of sodium thiosulphate, mark this bottle clearly and keep it out of the reach of children.
- Wash the skin and dry. Scrub the solution onto the affected parts of the skin with an old toothbrush or anything similar.
- In pityriasis versicolor, hypopigmented patches occur. These patches remain hypopigmented for some time, even if all the micro-organisms have been killed and the disease is fully treated. Repigmentation simply takes time. The presence of hypopigmented patches is, therefore, not an indication of a treatment failure.

precautions:
- Do not use the solution near the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of sodium thiosulphate solution have not been reported.

side effects:
- Side effects are not expected.

intoxication:
- Sodium thiosulphate is relatively non toxic.

Additional information

* Higher concentrations of sodium thiosulphate (up to 25%) are sometimes recommended. However, a 10% solution seems to be effective and is preferred.

* Sodium thiosulphate is used as an antidote in poisoning with iodine, cyanide and bleaching powder, and for treatment of silver nitrate chemical burns.

* Sodium thiosulphate is dispensed as crystals for dissolution at home because the solution is unstable. As soon as sodium thiosulphate has been dissolved, it should preferably be used within a week. Old solutions may be contaminated with micro-organisms which may cause infections.

● STRONG CORTICOSTEROID PREPARATION

● Formulation

Commercial preparation, containing for example clobetasol dipropionate or betamethasone dipropionate in a cream or ointment (marketed under various trade names). These corticosteroids are considered class 3 or 4.

packaging:
- See product specifications.

storage:
- See product specifications.
- The preparation should preferably be stored in a cool and dark place. It should be stored below the maximum storage temperature mentioned in the product specifications.
- Out of date corticosteroid preparations may be less effective.
- The preparation may get inhomogeneous at higher temperatures. If inhomogeneous, it should be mixed before dispensing or use.

● Therapy
- For external use only.
- These preparations contain very strong corticosteroids. They should only be used under medical supervision, for example in hospitals.
  Strong corticosteroids have very strong anti-inflammatory properties. They can be used for various skin diseases, for example psoriasis.

dose:
- See product specifications. Generally these preparations should be applied once or twice daily in a thin layer.
- General dose recommendation for strong corticosteroids: during the first week apply the strong corticosteroid preparation in a thin layer twice daily. After this week switch to either hydrocortisone cream or ointment, or apply the strong corticosteroid preparation twice a week and an indifferent vehicle twice daily during the remaining days. Emulsifying ointment, basic cream, calamine lotion, zinc paste and zinc oil may all be used as the indifferent vehicle.
- Do not use more than 30 grams a week.

instructions for use:
- See product specifications.
- The preparation should be applied in a thin layer.
- Do not cover with wrappings or bandages unless on doctor's instructions.

precautions:
- See product specifications.
- Do not use strong corticosteroid preparations on infections as these may worsen due to the corticosteroid.
- Apply strong corticosteroid preparations in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Corticosteroid preparations can only give symptomatic relieve. When treatment is stopped, the disease may return.
- In children growth retardation can result from using corticosteroid preparations. Regular control of both length and weight is recommendable for children during the use of strong corticosteroid preparations.
- Avoid contact of corticosteroid preparations with the eyes and the skin around the eyes.

pregnancy/lactation:
- High systemic doses of corticosteroids were found to be teratogenic in animal experiments. Corticosteroids are absorbed to some extend and they may pass the placenta and influence the fetus. However, harmful effects resulting from external use of strong corticosteroids have not been reported. Carefully evaluate the need for treatment during pregnancy.
- Corticosteroids are excreted in breast milk, but adverse effects on the baby due to external use of strong corticosteroids by the mother have not been reported. Carefully evaluate the need for treatment during lactation.
- See also the product specifications.

side effects:
- See product specifications.
- Corticosteroid preparations mask infections.
- Corticosteroid preparations may delay healing of damaged skin.
- Local side effects of corticosteroid preparations include thinning of the skin, irritation, an itching or burning sensation, and depigmentation. These effects are most likely to occur in the face, on hairy parts of the body, and in the genital region.
- Systemic side effects may result from the local use of strong corticosteroid preparations. They may be very serious, and include suppression of the corticosteroid synthesis in the adrenal glands.
- Sensitization reactions are rare but have been described. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* Strong corticosteroid preparations have a much stronger effect than hydrocortisone preparations. However, the skin gets used to treatment with the strong corticosteroid and in the long run even high doses have a reduced effect. This is called tachyphylaxis. Also, the risks of treatment with strong corticosteroid preparations are much higher than with hydrocortisone. Strong corticosteroid preparations should only be used if hydrocortisone is found to be ineffective. After the skin disease has been calmed, switch to hydrocortisone preparations or to twice weekly application of the strong corticosteroid.

● SULPHUR CREAM

contains: 2% sulphur in basic cream.

● Formulation

sulphur	2 g
basic cream	98 g

preparation:
1. If the sulphur contains large aggregates, rub it gently between two clean sheets of paper.
2. Triturate the sulphur with approximately 2 grams of basic cream.
3. Add the rest of the cream gradually and mix until completely homogeneous.

packaging:
- Sulphur cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The package should allow stirring of the cream.
- The cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, sulphur cream should be mixed until homogeneous before dispensing from stock.

storage:
- Sulphur cream should preferably be stored below 40°C.
- The cream should preferably be used within 3 months.
- Out of date creams risk being contaminated with micro-organisms which may cause infections.
- Sulphur cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not well closed, water may evaporate during storage. This results in a sulphur ointment like preparation with a sulphur content between 2 and 4%.

● Therapy
- For external use only.
- Sulphur cream has keratoplastic activity. It is also used because of its supposed antiseptic activity. The cream can be easily washed away from the skin and is suitable for use on hairy parts of the skin.
  Sulphur cream is used for scabies and pityriasis versicolor. Its use is sometimes recommended for acne, but drying preparations like salicylic acid solution and sulphur lotion are preferred.
  For the treatment of scabies, lindane cream is preferred, but sulphur may be useful for the treatment of scabies in small children. For the treatment of pityriasis versicolor sodium thiosulphate solution is preferred because it is cheaper and has better drying qualities.

dose:
- Apply the cream twice daily in a thin layer.

instructions for use:
- If inhomogeneous mix the cream before use.
- Apply sulphur cream in a thin layer after the skin has been washed.

precautions:
- Apply sulphur cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- The effect of sulphur on keratinization is difficult to predict. Keratolytic effects result in a decrease in blackheads, but sulphur may also exert a parakeratotic effect which increases the number of blackheads and worsens the acne.

pregnancy/lactation:
- Harmful effects resulting from external use of sulphur preparations have not been reported.

side effects:
- Sensitization due to methylparaben used as a preservative in the cream may occur but is rare with the concentration used in this cream. Sensitization due to yellow petrolatum may occur, but is rare.
  Irritation to lanette wax has been described. Inferior qualities of white petrolatum can cause irritation too.
  Sulphur itself may also cause skin irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* If larger quantities of sulphur cream are prepared with the intention to store them for some time, a freshly prepared basic cream should be used.

* Sulphur may be used in higher concentrations (up to 6%) in this cream.

* If basic cream is not available sulphur lotion or sulphur ointment may be used instead of the cream. The lotion has a more drying effect while the ointment has a more hydrating effect. For other alternative vehicles see sulphur ointment.

● SULPHUR LOTION
sulphur/calamine lotion

contains: 2% sulphur, 20% zinc oxide, 0.4% phenol in an aqueous vehicle.

● Formulation

sulphur		2	g
zinc oxide		20	g
bentonite		3	g
trisodium citrate		0,5	g
glycerin		5	ml
liquefied phenol		0,5	ml
water	to	100	ml

preparation:
1. Heat 100 ml of water to the boil and allow to cool. Use this water for the preparation of the lotion.
2. Dissolve the trisodium citrate in 70 ml of water.
3. If the sulphur contains large aggregates, rub it gently between two clean sheets of paper.
4. If sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
5. Mix the sulphur with the zinc oxide and with the bentonite.
6. Triturate this mixture with the glycerin and 20 ml of the citrate solution.
7. Add the rest of the citrate solution and mix until completely homogeneous.
8. Add the liquefied phenol and mix.
9. Add enough recently boiled and cooled water to produce 100 ml and mix well.

packaging:
- Sulphur lotion should be packed in well closed containers, which prevent evaporation of water and contamination with micro-organisms, and protect the lotion from exposure to light.
- Sulphur lotion should be shaken until homogeneous before dispensing from stock.

storage:
- Sulphur lotion should preferably be stored below 40°C.
- Sulphur lotion should preferably be used within 3 months.
- Out of date sulphur lotions may be less effective, and may be contaminated with micro-organisms which may cause infections.
- Sedimentation of solids may occur during storage. The lotion should always be shaken before dispensing or use.

● Therapy
- For external use only.
- Sulphur lotion has general soothing, cooling, antiseptic and antipruritic properties. It has a keratolytic effect which helps to prevent blackheads. It is used in acne, particularly in acne rosacea. However, the effect of sulphur on keratinization is difficult to predict. Sulphur may also exert a parakeratotic effect which increases the number of blackheads and worsens the acne. Therefore, salicylic acid solution is preferred in acne. Sulphur cream or ointment is not recommended for the treatment of acne because these preparations have a slight occlusive and hydrating effect.

dose:
- Apply the lotion twice daily. Therapy must generally be continued for several months.

instructions for use:
- Shake the lotion before use.
- Wash the skin with water and soap and allow to dry. Apply the lotion with some cottonwool or with a clean piece of cloth. Allow to dry and leave exposed to the air. Do not cover the affected parts with bandages.

precautions:
- Sulphur lotion should only be used on wounds with caution because of the risk of absorption of phenol.
- Sulphur lotion should not be used on large parts of the body or for periods longer than one week unless on doctor's instructions. Systemic side effects may result from absorption of phenol.
- Avoid contact of sulphur lotion with the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of sulphur preparations during pregnancy or lactation have not been reported.

side effects:
- The effect of sulphur on keratinization is difficult to predict. Keratolytic effects result in a decrease in blackheads, but sulphur may also exert a parakeratotic effect which increases the number of blackheads and worsens the acne.
- Sensitization reactions with a burning feeling are rare but may occur. If this occurs the use of the lotion should be stopped immediately.

intoxication:
- If sulphur lotion is ingested accidentally get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

● Additional information

* The formula is based on the modified calamine lotion included in this formulary. For more information on this formulation see calamine lotion.

* If sulphur lotion is prepared occasionally and dispensed immediately, it may be prepared in a much simpler way than mentioned above. Triturate 2 grams of sulphur gradually with 98 grams of ready for use calamine lotion.

* Other concentrations of sulphur (up to 6%) may be used.

● SULPHUR OINTMENT

contains: 2% sulphur in emulsifying ointment.

● Formulation

sulphur	2 g
emulsifying ointment	98 g

preparation:
1. If the sulphur contains large aggregates, rub it gently between two clean sheets of paper.
2. Triturate the sulphur with approximately two grams of emulsifying ointment.
3. Add the rest of the ointment gradually and mix until completely homogeneous.

packaging:
- Sulphur ointment should be packed in a container which allows stirring of the ointment. The ointment should not be packed in collapsible tubes when the storage temperature may exceed 25°C.
- If inhomogeneous, sulphur ointment should be mixed until homogeneous before dispensing from stock.

storage:
- The ointment should preferably be stored below 25°C.
- The ointment should preferably be used within 2 years.
- Ointments older than 2 years may show a changed consistency and may be less effective.
- Sulphur ointment may get inhomogeneous at temperatures of 25°C and above. Inhomogeneity does not affect the ointment, provided that it is properly mixed before dispensing or use.

● Therapy
- For external use only.
- Sulphur ointment has keratoplastic and possibly antiseptic activity. The ointment can be washed away from the skin and is suitable for use on hairy parts of the skin, although sulphur cream is preferred in this case.
  Sulphur ointment is used for scabies and pityriasis versicolor. Its use is not recommended for acne because of its hydrating properties. For acne drying preparations like salicylic acid solution and sulphur lotion are preferred.
  In scabies lindane cream is preferred, but sulphur ointment may be useful for the treatment of scabies in small children. For the treatment of pityriasis versicolor, sodium thiosulphate is preferred because it is cheaper and has a drying effect.

dose:
- Apply the ointment twice daily in a thin layer until the condition has cleared.

instructions for use:
- If inhomogeneous mix the ointment before use.
- Wash the skin with water and soap and allow to dry. Apply sulphur ointment in a thin layer.

precautions:
- The effect of sulphur on keratinization is difficult to predict. Keratolytic effects result in a decrease in blackheads, but sulphur may also exert a parakeratotic effect which increases the number of blackheads and worsens the acne.
- Sulphur ointment should be applied in a thin layer. Thick layers have occlusive and hydrating properties which may cause infections and exacerbation of the skin disease.

pregnancy/lactation:
- Harmful effects resulting from external use of sulphur preparations during pregnancy or lactation have not been reported.

side effects:
- Sulphur ointment may cause an increase in blackheads and an exacerbation of acne.
- Sensitization due to yellow petrolatum may occur but is rare. If sensitization occurs the use of the ointment should be stopped.
  Irritation to lanette wax has been described. Inferior qualities of white petrolatum may cause irritation too.
  Sulphur itself may cause some skin irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* If larger quantities of sulphur ointment are prepared with the intention to store them for some time, a freshly prepared emulsifying ointment should preferably be used.

* Sulphur may be used in higher concentrations (up to 6%) in this ointment.

* If emulsifying ointment is not available, sulphur lotion or sulphur cream may be used instead. The lotion has a drying effect while the cream has a slightly hydrating effect.
  If these are not available, sulphur may be incorporated in petrolatum with 10% wool fat. This, however, is an occlusive preparation with a high sensitization potential. Zinc paste is another alternative vehicle for sulphur, this is less active but relatively non occlusive.

● TAR CREAM

contains: 3% coal tar in basic cream.

● Formulation

coal tar	3 g
basic cream	97 g

preparation:
1. Mix the coal tar carefully with approximately 20 grams of the cream.
2. Add the rest of the cream gradually and mix until completely homogeneous.

packaging:
- Tar cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The package should allow stirring of the cream. Tar cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, tar cream should be mixed until homogeneous before dispensing from stock.

storage:
- Tar cream should preferably be stored below 40°C.
- The cream should preferably be used within 3 months.
- Out of date creams risk being contaminated with micro-organisms which may cause infections.
- Tar cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not well closed, water may evaporate during storage. This results in an emulsifying ointment type preparation with a tar content between 3 and 6%.

● Therapy
- For external use only.
- Tars are keratoplastic agents with weak antiseptic and antipruritic effects. They can be used in psoriasis and eczema. Tar cream has only slightly moisturizing effects.
  The preparation is washable and may be used on hairy parts of the skin. Coal tar can also be incorporated in an alcoholic solution, which gives a more drying preparation, and in zinc paste, which produces a more protective preparation.

dose:
- Apply twice daily to the affected parts of the skin.

instructions for use:
- If inhomogeneous, mix the cream before use.
- Wash the skin carefully before application. Apply the cream to the affected parts of the skin in a thin layer. Rub it gently into the skin.

precautions:
- Tar preparations stain the skin, clothes and bedding.
- Tars have a phototoxic effect. Exposure to sunlight should be avoided during tar therapy, at least until 24 hours after the last application.
- Avoid application to large skin surfaces and healthy parts of the skin.
- Apply tar cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.

pregnancy/lactation:

- Harmful effects resulting from external use of tar preparations during pregnancy or lactation have not been reported, but safety has not been proven. Carefully evaluate the need for treatment and the possible risks during pregnancy or lactation. Other preparations used in psoriasis (dithranol, strong corticosteroids, oral etretinate) constitute higher risks during pregnancy. Pregnancy itself may have a beneficial effect on psoriasis.

side effects:

- Tar preparations may cause skin irritation and folliculitis. Irritation may also be due to lanette wax or to inferior qualities of white petrolatum used in the cream.
  Coal tar has a low sensitization potential. Sensitization due to methylparaben may develop but is rare with the concentration used in this cream. Sensitization due to yellow petrolatum may occur but is rare. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* Larger quantities of coal tar can be incorporated in this cream, but will affect the stability of the cream.

* If larger quantities of tar cream are prepared with the intention to store them for some time, a freshly prepared basic cream should be used.

* If basic cream is not available, tar paste or tar solution may be used. Emulsifying ointment, petrolatum with 10% wool fat, or plain petrolatum are less suitable vehicles because they are occlusive, but they may be used if basic cream is not available.

● TAR PASTE

contains: 5% coal tar in zinc paste.

● Formulation

coal tar	5 g
zinc paste	95 g

preparation:
1. Mix the coal tar carefully with approximately 10 grams of zinc paste. Gentle heat may be used.
2. Add the rest of the paste gradually and mix until completely homogeneous.

packaging:
- The paste should be packed in a well closed container with a wide opening to make it easy to remove the paste from the container. Collapsible tubes are not appropriate as it may be difficult to remove the paste from such tubes.

storage:
- Tar paste should preferably be stored below 40°C.
- Tar paste should preferably be used within 2 years.
- Out of date pastes may be less effective and may have a changed consistency. However, if they are not too old, they may still be used.

● Therapy
- For external use only.
- Tars are keratoplastic agents with weak antiseptic and antipruritic activity. They are useful for the treatment of psoriasis and eczema. Tar paste has a protective effect. Coal tar can also be incorporated in a cream to give a more penetrating preparation or in a solution to give a more drying preparation.
  Tar paste is very difficult to wash away from the skin. This makes it unsuitable for use on hairy parts of the skin.

dose:
- Apply the paste twice daily to the affected parts of the skin.

instructions for use:
- Wash the skin carefully before application.
- Apply the paste in a layer just thick enough to provide adequate protection.
  A loose bandage may be used to give more protection and to keep the paste in place.
- To remove the paste rinse with some vegetable oil first.

precautions:
- Tar preparations stain the skin, clothes and bedding.
- Tars may have a phototoxic effect. Exposure to sunlight should be avoided during tar therapy, at least until 24 hours after the last application.
- Avoid application to large skin surfaces and healthy parts of the skin.

pregnancy/lactation:

- Harmful effects resulting from external use of tar preparations during pregnancy or lactation have not been reported, but safety has not been proven. Carefully evaluate the need for treatment and the possible risks during pregnancy or lactation. Other preparations used in psoriasis (dithranol, strong corticosteroids, oral etretinate) constitute higher risks during pregnancy. Pregnancy itself may have a beneficial effect on psoriasis.

side effects:

- Tar preparations may cause skin irritation and folliculitis. Irritation may also be due to inferior qualities of white petrolatum used in the paste.
  Coal tar has a low sensitization potential. Sensitization due to yellow petrolatum may occur but is rare. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* Lower concentrations of tar may be prepared by further diluting the paste.

* If larger quantities are prepared with the intention to store them for some time, a freshly prepared zinc paste should preferably be used.

* If zinc paste is not available, tar solution or tar cream may be used instead. Emulsifying ointment, petrolatum with 10% wool fat, or plain petrolatum are less suitable vehicles because they are occlusive, but they may be used if better vehicles are not available.

● TAR SOLUTION

contains: 20% coal tar in an alcoholic solution.

● Formulation

coal tar		20	g
polysorbate 80		5	g
industrial methylated spirit 95%	to	100	ml

preparation:
1. Mix the coal tar with the polysorbate 80.
2. Pour this mixture into about 80 ml of industrial methylated spirit 95%. Shake this mixture occasionally during one hour.
3. Allow to stand for 24 hours.
4. Decant and filter.
5. Add enough industrial methylated spirit to produce 100 ml and mix well.

packaging:
- Tar solution should be packed in a well closed container.

storage:
- Tar solution should be stored under cool conditions.
- Tar solution is highly flammable. Do not store in hot places or near open flames. Do not smoke in places where tar solution is stored.
- Tar solution should preferably be used within 3 months.
- Out of date tar solutions may have a higher tar content due to evaporation of alcohol. Such solutions should not be used.
  Evaporation of alcohol may occur if the package is not well closed. This results in a solution with a higher tar content.

● Therapy

- For external use only.
- Tars are keratoplastic agents with weak antiseptic and antipruritic effects. They are useful for the treatment of psoriasis and eczema. Tar solution has a drying effect.
  Tar solution is washable and consequently it is suitable for use on hairy parts of the skin. Coal tar can be incorporated in a cream, to give a more penetrating preparation or in a paste to produce a more protective preparation.

dose:
- Apply the solution to the affected parts of the skin twice daily.

instructions for use:
- Wash the skin carefully. Apply the solution to the skin. Do not cover with a bandage.

precautions:
- Tar preparations stain the skin, clothes and bedding.
- Tar solution is highly flammable.
- Tars may have a phototoxic effect. Exposure to sunlight should be avoided during tar therapy, at least until 24 hours after the last application.
- Avoid application to large skin surfaces and healthy parts of the skin.

pregnancy/lactation:
- Harmful effects resulting from external use of tar preparations during pregnancy or lactation have not been reported, but safety has not been proven. Carefully evaluate the need for treatment and the possible risks during pregnancy or lactation. Other preparations used in psoriasis (dithranol, strong corticosteroids, oral etretinate) constitute higher risks during pregnancy. Pregnancy itself may have a beneficial effect on psoriasis.

side effects:
- Tar preparations may cause skin irritation and folliculitis. Irritation may also be due to the alcohol.
  Coal tar has a low sensitization potential. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

intoxication:
- After accidental ingestion get medical advice. The clinical picture after such ingestion is very complicated as intoxication is due to tar, ethanol and methanol. While waiting for a doctor induce vomiting with syrup of ipecacuanha and bring a 5% sodium bicarbonate solution in the stomach.

● Additional information

* This formula is equivalent to the formula of the British Pharmacopoeia. Various other, slightly different formulations are given in other pharmacopoeias.

* Lower concentrations of tar may be used.

* The solution contains only the soluble ingredients of the tar that have been extracted. Therefore, it may be less effective than other tar preparations such as creams. This relative effectiveness also depends on the exact composition of the tar used.

* If tar solution is not available, tar cream or tar paste may be used instead. Emulsifying ointment, petrolatum with 10% wool fat, or plain petrolatum are less suitable vehicles because they are occlusive, but they may be used if better vehicles are not available.

● UREA CREAM

contains: 10% urea in basic cream

● Formulation

urea	10 g
water	15 g
basic cream	75 g

preparation:
1. Heat 30 ml of water to the boil and allow to cool. Use this water for the preparation.
2. Dissolve the urea in 15 ml of this water.
3. Mix the urea solution carefully with the cream until completely homogeneous.

packaging:
- Urea cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The package should allow stirring of the cream. Urea cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, urea cream should be mixed until homogeneous before dispensing from stock.

storage:
- The cream should be stored in a cool place.
- The cream should preferably be used within 1 month.
- Out of date creams may be less effective due to degradation of urea. The odour of ammonia is an indication for such degradation.
  Out of date creams also risk being contaminated with micro-organisms which may cause infections.
- Urea cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not closed well, water may evaporate during storage. This results in a cream with a lower water content and a higher urea content. Such creams are more effective but they will also produce more frequent side effects. Eventually, evaporation of water can result in a useless mixture of fatty constituents and crystalline urea that should be discarded.

● Therapy
- For external use only.
- Urea cream has strong moisturizing properties. It can be used to hydrate the skin, for example in ichthyosis. Urea cream is easily washed away from the skin.
  For simple dry skin problems a less powerful and cheaper emollient is preferred, such as emulsifying ointment or even petrolatum.
  Urea cream is somewhat less effective but better tolerated than urea ointment.

dose:
- Apply in a thin layer twice daily.

instructions for use:
- Wash the skin carefully with water and soap. Hydrate the skin by keeping it wet for 10 to 15 minutes, for example by taking a bath. If the cream is inhomogeneous, mix it before use. Apply the cream in a thin layer.
- It may take several days before results can be seen.

precautions:
- Do not apply urea cream near the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of urea cream have not been reported.

side effects:
- Urea cream may produce a burning feeling, particularly when used in the face or on broken skin. This is no reason to stop treatment.
- Sensitization due to methylparaben may occur, but is rare with the concentration used in this cream. Sensitization due to yellow petrolatum may occur, but is rare.
  Irritation due to lanette wax has been described. Inferior qualities of white petrolatum may also cause irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* This formula is analogous to the formula given in the Formulary of Dutch Pharmacists. It is based on the formulation of basic cream. For more information on the formulation and alternative starting materials refer to the monograph on basic cream.

● UREA OINTMENT

contains: 10% urea in emulsifying ointment

● Formulation

urea	10 g
water	20 g
emulsifying ointment	70 g

preparation:
1. Heat 40 ml of water to the boil and allow to cool. Use this water for the preparation.
2. Dissolve the urea in 20 ml of this water.
3. Mix the urea solution carefully with the emulsifying ointment, by small quantities at a time, until completely homogeneous.

packaging:
- Urea ointment should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The package should allow stirring of the ointment.
  Urea ointment should not be packed in collapsible tubes when the storage temperature may exceed 25°C.
- If inhomogeneous, urea ointment should be mixed until homogeneous before dispensing from stock.

storage:
- The ointment should preferably be stored in a cool place.
- The ointment should preferably be used within 1 month.
- Urea ointment may get inhomogeneous at temperatures of 25°C and above. Inhomogeneity does not affect the ointment, provided that it is properly mixed before dispensing or use.
- Out of date ointments may be less effective due to degradation of urea. The odour of ammonia is an indication for such degradation.
  Out of date ointments also risk being contaminated with micro-organisms which may cause infections.
- If the package is not closed well, water may evaporate during storage. This results in a useless mixture of fatty constituents and crystalline urea that should be discarded.

● Therapy
- For external use only.
- Urea ointment has strong moisturizing properties. It can be used to hydrate the skin, for example in ichthyosis. Urea ointment is easily washed away from the skin.
  For simple dry skin problems a less powerful and cheaper emollient is preferred, such as emulsifying ointment or even petrolatum.
  Urea ointment is somewhat more effective, but less well tolerated than urea cream.

dose:
- Apply in a thin layer twice daily.

instructions for use:
- Wash the skin carefully with water and soap. Hydrate the skin by keeping it wet for 10 to 15 minutes, for example by taking a bath. If inhomogeneous, mix the ointment before use. Apply the ointment in a thin layer.
- It may take several days before results can be seen.

precautions:
- Do not apply urea ointment near the eyes.

pregnancy/lactation:
- Harmful effects resulting from external use of urea ointment have not been reported.

side effects:
- Urea ointment may produce a burning feeling, particularly when used in the face or on broken skin. This is no reason to stop treatment.
- Sensitization due to yellow petrolatum may occur, but is rare.
  Irritation due to lanette wax has been described. Inferior qualities of white petrolatum may also cause irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

● Additional information

* This formula is analogous to the formula given in the Formulary of Dutch Pharmacists. It is based on the formulation of emulsifying ointment. For more information on the formulation and alternative starting materials see the monograph on emulsifying ointment.

● WATER

● Formulation

water

preparation:
1. The water should be of at least potable quality. Heat the water to the boil and allow to cool. Cover the container loose during cooling.

package:
- Water should be kept in a clean and well closed container.

storage:
- Water should always be freshly boiled and cooled.
- When allowing water to cool, the container should be covered loose, to prevent micro-organisms or dust particles to fall into the water. Covering should preferably be done with a glass watch.
- Water that has been stored, even for a limited time, may be contaminated with micro-organisms. These may cause infections if such water is applied to the skin.

● Therapy
- Water has general cooling properties. It can be used in various skin diseases. It can be used with compresses.

● WHITFIELD'S CREAM

benzoic and salicylic acid cream

contains: benzoic acid 5% and salicylic acid 5% in basic cream.

● Formulation

benzoic acid	5 g
salicylic acid	5 g
basic cream	90 g

preparation:

1. Grind the benzoic acid and the salicylic acid. If sieves are available, sieve the benzoic acid and the salicylic acid, preferably through a 90 µm sieve.
2. Mix the benzoic acid with the salicylic acid.
3. Triturate this mixture with approximately 10 grams of basic cream.
4. Add the rest of the cream gradually and mix until completely homogeneous.

packaging:

- The cream should be packed in a well closed container, which prevents evaporation of water and contamination with micro-organisms. The container should allow stirring of the cream. Whitfield's cream should not be packed in collapsible tubes when the storage temperature may exceed 40°C.
- If inhomogeneous, Whitfield's cream should be mixed until homogeneous before dispensing from stock.

storage:

- Whitfield's cream should preferably be stored below 40°C.
- The cream should preferably be used within 3 months.
- Out of date creams may be less effective and risk being contaminated with micro-organisms which may cause infections.
- Whitfield's cream may get inhomogeneous at temperatures of 40°C and above. Inhomogeneity does not affect the cream, provided that it is properly mixed before dispensing or use.
- If the package is not closed well, water may evaporate during storage. This results in a preparation like Whitfield's ointment which has, however, a higher benzoic acid and salicylic acid content. Such preparations may be more sensitizing and more irritating.

● Therapy

- For external use only.
- Whitfield's cream combines a fungistatic activity with keratolytic properties. It is useful for treating superficial skin infections caused by fungi, such as ringworm and athlete's foot. Candida species are not sensitive.
  The cream is less hydrating than the ointment and is preferred in most cases. Non responsive cases may be treated with miconazole cream.

dose:

- The cream should be applied in a thin layer to the affected parts of the skin twice daily. Treatment may take several weeks.

instructions for use:

- Wash the skin with water and soap. Apply the cream in a thin layer and rub it into the skin. Whitfield's cream should only be applied to affected parts of the skin.

precautions:
- In small children, do not use the cream on large parts of the body or for prolonged periods of time.
- Apply Whitfield's cream in a thin layer. Excessively thick layers have occlusive and hydrating properties, which may cause infections and exacerbation of the skin disease.
- Do not use the cream for a patient who is known to be allergic to one of the constituents. If sensitization reactions develop, the use of the cream should be stopped immediately.
- Ringworm and athlete's foot are highly contagious. If possible, close contacts (family, school) should be examined.
- Good personal hygiene and careful drying of the skin are essential to prevent reinfection.

pregnancy/lactation:
- Teratogenic effects after the use of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans due to external use of salicylic acid have not been described. Evaluate benefit/risk before using salicylic acid during pregnancy.
- After external use of salicylic acid containing preparations by the mother, salicylic acid is excreted in the breast milk. However, no adverse effects on the child have been reported after external use of salicylic acid by the mother. Evaluate benefit/risk before using salicylic acid during lactation.

side effects:
- Sensitization may occur. Constituents that may cause sensitization include benzoic acid and salicylic acid, which are used as active ingredients, methylparaben, which is used as a preservative and yellow petrolatum.
  Irritation due to salicylic acid, lanette wax or inferior qualities of petrolatum may occur but are rare. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.
- Salicylic acid inhibits blood coagulation. This effect is not likely to be a practical problem after external use of Whitfield's cream. People with blood coagulation problems (e.g. users of anticoagulants) should only use salicylic acid containing preparations under close medical supervision.

intoxication:
- Excessive or long term use of salicylic acid containing preparations may cause systemic intoxication. This is not likely to occur after the use of salicylic acid containing preparations on the skin, with the exception of long term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Such systemic intoxication is characterised by:
- slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
- more severe intoxication: excitation, confusion, fever and convulsions.
- severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.
  If such effects occur, the use of the preparation should be stopped immediately.

Additional information

* The formula mentioned above differs from that of the Whitfield preparations generally used in Anglo-Saxon countries. The latter contain 6% benzoic acid and 3% salicylic acid. The 5/5% formulation may be slightly more active.

* If no basic cream is available, emulsifying ointment may be used. For information on other alternative vehicles see under "Whitfield's ointment".

* If large quantities are prepared with the intention to store them for some time, a freshly prepared basic cream should be used.

● WHITFIELD'S OINTMENT

benzoic and salicylic acid ointment.

contains: benzoic acid 5% and salicylic acid 5% in emulsifying ointment.

● Formulation

benzoic acid	5 g
salicylic acid	5 g
emulsifying ointment	90 g

preparation:

1. Grind the benzoic acid and the salicylic acid. If sieves are available, sieve the benzoic acid and the salicylic acid, preferably through a 90 µm sieve.
2. Mix the benzoic acid with the salicylic acid.
3. Triturate this mixture with approximately 10 grams of emulsifying ointment until homogeneous.
4. Add the rest of the ointment gradually and mix until completely homogeneous.

packaging:

- The ointment should be packed in a container which allows stirring of the ointment. Whitfield's ointment should not be packed in collapsible tubes when the storage temperature may exceed 25°C.
- If inhomogeneous, Whitfield's ointment should be mixed until homogeneous before dispensing from stock.

storage:

- Whitfield's ointment should preferably be stored below 25°C.
- The ointment should preferably be used within 2 years.
- Out of date ointment may be less effective.
- Whitfield's ointment may get inhomogeneous at temperatures of 25°C and above. Inhomogeneity does not affect the ointment, provided that it is properly mixed before dispensing or use.

● Therapy

- For external use only.
- Whitfield's ointment combines a fungistatic activity with keratolytic properties. It is useful for treating superficial skin infections caused by fungi, such as ringworm and athlete's foot. Candida species are not sensitive.
  The cream is less hydrating than the ointment and is preferred in most cases.

dose:

- The ointment should be applied in a thin layer to the affected parts of the skin twice daily. Treatment may take several weeks.

instructions for use:

- Wash the skin with water and soap. Apply the ointment in a thin layer and rub it into the skin. Whitfield's ointment should only be applied to affected parts of the skin.

precautions:
- If applied in a thick layer, the ointment has an occlusive, hydrating effect. This should be avoided. Because of the occlusive effect, the use of the ointment in skin folds should be avoided and the cream should be used instead.
- In small children, do not use the ointment on large parts of the body or for prolonged periods of time.
- Do not use the ointment for a patient who is known to be allergic to one of the constituents. If sensitization reactions develop, the use of the ointment should be stopped immediately.
- Ringworm and athlete's foot are highly contagious. If possible, close contacts (family, school) should be examined.
- Good personal hygiene and careful drying of the skin are essential to prevent reinfection.

pregnancy/lactation:
- Teratogenic effects after the use of salicylates in high oral doses have been shown in animal studies. Harmful effects in humans due to external use of salicylic acid have not been described. Evaluate benefit/risk before using salicylic acid during pregnancy.
- After external use of salicylic acid containing preparations by the mother, salicylic acid is excreted in the breast milk. However, no adverse effects on the child have been reported after external use of salicylic acid by the mother. Evaluate benefit/risk before using salicylic acid during lactation.

side effects:
- Sensitization may occur but is not common. It may be due to salicylic or benzoic acid or to yellow petrolatum.
  Irritation due to lanette wax or to inferior qualities of white petrolatum may occur but are uncommon. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.
- Salicylic acid inhibits blood coagulation. This effect is not likely to be a practical problem after external use of Whitfield's cream. People with blood coagulation problems (e.g. users of anticoagulants) should only use salicylic acid containing preparations under close medical supervision.

intoxication:
- Excessive or long term use of salicylic acid containing preparations may cause systemic intoxication. This is not likely to occur after the use of salicylic acid containing preparations on the skin, with the exception of long term use on large areas of the skin. Children are more vulnerable to systemic intoxication because they have a relatively large skin surface. Such systemic intoxication is characterised by:
- slight intoxication: sweating, abdominal pains, dehydration and loss of hearing.
- more severe intoxication: excitation, confusion, fever and convulsions.
- severe intoxication: respiratory alkalosis followed by a metabolic acidosis and CNS depression, resulting in coma and death.
  If such effects occur, the use of the preparation should be stopped immediately.

Additional information

* The preparation mentioned above differs from the Whitfield preparations generally used in Anglo-Saxon countries. The latter contain 6% benzoic acid and 3% salicylic acid. The 5/5% formulation may be slightly more active.

* If no emulsifying ointment is available, petrolatum with 10% wool fat may be used instead. This results in an ointment that is not washable, and that may be more sensitizing.
The use of plain petrolatum as a vehicle for Whitfield's ointment is also possible, but this results in a rather occlusive ointment. This occlusion may cause hydration of the infected skin and a subsequent exacerbation of the disease.

* If large quantities are prepared with the intention to store them for some time, a freshly prepared emulsifying ointment should preferably be used.

● ZINC OIL

zinc oxide liniment

contains: 60% zinc oxide in vegetable oil

● Formulation

zinc oxide	60 g
vegetable oil	40 g

preparation:
1. If sieves are available, sieve the zinc oxide, preferably through a 90 μm sieve.
2. Triturate the zinc oxide with the vegetable oil.
3. Mix until completely homogeneous.

packaging:
- Zinc oil should be packed in airtight containers. As zinc oil attacks certain plastics, it should not be packed in plastic containers. Glass is most appropriate. The container should allow stirring of the zinc oil.
- If inhomogeneous, zinc oil should be mixed until homogeneous before dispensing from stock.

storage:
- Zinc oil should preferably be stored below 40°C.
- Zinc oil should preferably be used within 3 months.
- Out of date zinc oil is not easily applied to the skin.

● Therapy

- For external use only.
- Zinc oil has a general soothing effect and is used in various skin diseases.

dose:
- Apply zinc oil several times daily to the skin.

instructions for use:
- Zinc oil should be stirred before use.
- Zinc oil can be removed from the skin with water and soap, but this is difficult. The use of vegatable oil to rinse the skin may be easier.

precautions:
- Zinc oil should not be used on hairy parts of the skin because it is difficult to remove.

pregnancy/lactation:
- Harmful effects due to external use of zinc oil have not been reported.

side effects:
- Sensitization may occur but is rare. The sensitization potential depends largely on the type of oil used. If sensitization reactions develop, stop using this preparation and do not use it again.

Additional information

* Several pharmacopoeias recommend the addition of some oleic acid. This has a beneficial effect on the consistency of the preparation, but is not essential. On the other hand, too much oleic acid gives a less stable preparation. Vegetable oils contain a certain amount of free oleic acid. The oleic acid content rises during storage, especially at higher temperatures. Oleic acid is therefore omitted from the formula.

* In this preparation, mineral oil (liquid paraffin) cannot be used instead of vegetable oil, because this would result in a preparation with a different therapeutic effect.

● ZINC PASTE

zinc oxide paste

contains: 50% zinc oxide in petrolatum.

● Formulation

zinc oxide	50 g
petrolatum	50 g

preparation:

1. If sieves are available, sieve the zinc oxide, preferably through a 90 µm sieve.
2. Melt the petrolatum over gentle heat.
3. Triturate the zinc oxide with the petrolatum.
4. Mix until no zinc oxide aggregates are left and the preparation is completely homogeneous.

packaging:

- Zinc paste does not require a special package. Packaging with a wide opening is preferred as it is easier to take the paste out. Collapsible tubes are not appropriate as it may be difficult to remove the paste from them.

storage:

- Zinc paste does not require special storage conditions.
- Zinc paste should preferably be used within 2 years.
- Out of date pastes may be used as long as the consistency of the preparation remains satisfactory.

● Therapy

- For external use only.
- Zinc paste has good protective properties without being too occlusive. Due to its high powder content, zinc paste may have a drying effect on the skin. It can be used in the healing process of clean ulcers, e.g. in leprosy.
  As the zinc oxide particles in the paste reflect sunlight, zinc paste is an effective sun blocking preparation.
  Zinc paste is also used as a vehicle for tar and dithranol.

dose:

- Apply zinc paste several times daily to the skin.

instructions for use:

- Zinc paste should be applied to the skin or the clean ulcer in a layer just thick enough to provide adequate protection. The paste layer may be covered with a loose bandage.
- Zinc paste is very difficult to remove from the skin. It should therefore not be used on hairy parts of the skin. To remove zinc paste from the skin rinse with some vegetable oil before using water and soap.

pregnancy/lactation:

- Harmful effects resulting from external use of zinc paste have not been reported.

side effects:

- Yellow petrolatum may cause sensitization reactions. Sensitization reactions to white petrolatum are very rare. White petrolatum of inferior quality, however, may cause irritation. If sensitization or severe irritation reactions develop, stop using this preparation and do not use it again.

Additional information

* The formula for zinc paste was adapted from a formula used in many pharmacopoeias. The original formula contains 25% zinc oxide, 25% starch and 50% paraffins. Starch, however, is not an appropriate material for use in hot and humid climates due to its generally high microbial contamination. The paste with 50% zinc oxide has the same general characteristics.

6 Raw materials

This section contains information on all raw materials mentioned in the preparation monographs. Each raw materials monograph may contain the following headings:

● Title

synonyms

description:
a description of appearance, colour and smell.

qualities/varieties:
information on various qualities marketed, their differences and suitability for use in the preparations included in this formulary.

density:
the density of the material (at 20°C, for fluids only), to convert weight to volume and volume to weight.

package:
information on package requirements.

storage:
information on storage requirements, stability, signs of degradation (if any), and risks associated with the use of out of date raw materials. The term "should" is used to indicate absolutely necessary requirements, while "should preferably" indicates strongly recommended procedures. When indicated that a raw material should be kept cool, this means a storage temperature below 15°C is recommended.

hazards/toxicity:
information on special hazards (fire and explosive hazards) and systemic and local toxicity; information on how to treat a person after accidental skin or eye contact or after accidental ingestion, and, if relevant, information on environmental hazards.

● Aluminium magnesium silicate

magnesium aluminium silicate, saponite.

description:

Aluminium magnesium silicate is an odourless, creamy-white powder or small flakes.

qualities/varieties:

Aluminium magnesium silicate is marketed in various grades. For use in dermatological preparations a pharmaceutical grade is required. Aluminium magnesium silicate is marketed under various trade names, such as Veegum (UK, US), Dianeusine (F) and Sicco-gynaedron (BRD).

package:

Aluminium magnesium silicate does not require a special package.

storage:

Aluminium magnesium silicate does not require special storage conditions and has a practically indefinite shelf life.

hazards/toxicity:

Inhalation of dust particles should be avoided but aluminium magnesium silicate does not cause asbestosis.

● Ascorbic acid

vitamin C

description:

Ascorbic acid consists of odourless and colourless crystals or a white to slightly yellowish powder.

package:

Ascorbic acid should be packed in airtight, non metallic containers, which protect the ascorbic acid from exposure to direct sunlight.

storage:

Ascorbic acid should be protected from exposure to direct sunlight. It should be used before the expiry date. Out of date ascorbic acid is less effective.

● Bentonite

mineral soap, soap clay, wilkinite.

description:

Bentonite is an odourless fine, greyish-white powder with a yellowish tint, or pale-buff coloured.

qualities/varieties:

Bentonite is marketed in different qualities. For use in dermatological preparations a pharmaceutical grade is required.

package:

Bentonite should be packed in airtight containers.

storage:
No special storage conditions are required. The shelf life of bentonite is practically indefinite. Bentonite may absorb moisture from the air. It usually contains bacterial spores. If bentonite gets wet, the microbial count may get higher.

hazards/toxicity:
Inhalation of dust particles should be avoided, but bentonite does not cause asbestosis.

● Benzoic acid

description:
Benzoic acid consists of colourless feathery crystals, white scales or a white powder with a slight characteristic odour.

package:
Benzoic acid should be packed in airtight containers.

storage:
Benzoic acid does not require special storage conditions. It should preferably be used before the expiry date. Out of date benzoic acid may be less effective.

hazards/toxicity:
Benzoic acid is relatively non toxic.
Avoid inhalation of dust particles, these are irritating.

● Benzylbenzoate

description:
Benzylbenzoate is a clear colourless oily liquid with a faint characteristic odour. At temperatures below 18°C it may crystallize.

density:
1 ml = 1.12 g 1 g = 0.89 ml

package:
Benzylbenzoate should be packed in well filled, airtight containers, which provide adequate protection against exposure to light.

storage:
Benzylbenzoate should preferably be stored below 40°C. Benzylbenzoate should preferably be used before the expiry date. Out of date benzylbenzoate may be less effective.

hazards/toxicity:
Benzylbenzoate causes central nervous system depression after ingestion. Convulsions may result. After accidental ingestion induce vomiting with syrup of ipecacuanha. Diazepam injections may be needed to treat convulsions.

● Calamine

description:
Calamine is a reddish-brown amorphous powder. It is odourless.

qualities/varieties:
In many pharmacopoeias, for example in the British Pharmacopoeia, calamine is defined as a basic zinc carbonate, coloured with ferric oxide. Some pharmacopoeias however, specify a different material. The United States Pharmacopoeia defines calamine as zinc oxide coloured with ferric oxide.
Both qualities are equivalent. Pharmaceutical calamine does not need grinding or sieving.

package:
Calamine should be packed in an airtight container.

storage:
Calamine should be kept dry. As long as calamine is kept dry, it has a practically indefinite shelf life.

hazards/toxicity:
Inhalation of calamine should be avoided, but calamine does not cause asbestosis.

● Chlorhexidine diacetate

description:
Chlorhexidine diacetate is a white to pale-cream coloured, almost odourless crystalline powder.

package:
Chlorhexidine diacetate should be packed in airtight containers, which provide adequate protection against exposure to light. Cork closures should not be used.

storage:
Chlorhexidine diacetate does not require special storage conditions. It should be protected from light. Chlorhexidine diacetate should preferably be used before the expiry date. Out of date chlorhexidine may be less effective.

hazards/toxicity:
Chlorhexidine diacetate is poorly absorbed from the gastro-intestinal tract and hence is relatively non toxic. After accidental ingestion induce vomiting with syrup of ipecacuanha.

● Chlorhexidine digluconate stock solution 20%

description:
Chlorhexidine digluconate stock solution 20% is a colourless to pale straw coloured almost odourless liquid. It may be clear or slightly opalescent.

qualities/varieties:
A commercial chlorhexidine digluconate 5% solution is marketed in some countries. It contains a nonionic surfactant and a red colouring agent. Such solutions offer no advantages for general use. The chlorhexidine digluconate stock solution 20% is recommended.

density:
of the chlorhexidine digluconate stock solution 20%:
1 ml = 1.06 g 1 g = 0.94 ml.

package:
Chlorhexidine digluconate stock solution 20% should be packed in airtight containers, which provide adequate protection against exposure to light.

storage:
Chlorhexidine digluconate stock solution 20% should preferably be kept below 25°C. It should be protected from light. It should be used before the expiry date. Out of date chlorhexidine digluconate stock solution 20% may be less effective.

hazards/toxicity:
Chlorhexidine digluconate is poorly absorbed from the gastro-intestinal tract and hence is relatively non toxic. After accidental ingestion induce vomiting with syrup of ipecacuanha.

● Coal tar

pix lithantracis, pix carbonis

description:
Tar is a dark brown to black viscous liquid with a characteristic smell. It consists of a complex mixture.

qualities/varieties:
Tars may be obtained from the destructive distillation of coal (coal tar, pix lithantracis, pix carbonis) or wood (wood tar, pine tar, pix pini, pix liquida, Stockholm tar). Coal tar is more effective, but it may cause phototoxic reactions. Coal tar has a low sensitization potential. In contrast, wood tar is less effective, has a higher sensitization potential, but does not cause phototoxic reactions. To differentiate between the two types of tar, shake some of the tar with water. The water will show an acidic reaction in the case of wood tar, and an alkaline reaction in the case of coal tar. Both coal tar and wood tar show variations in composition, but this does not seem to influence the activity or safety of the tar. Coal tar is preferred over wood tar because it is more effective and less sensitizing.

package:
Tars should be packed in airtight containers.

storage:
Tars should preferably be kept cool. They should preferably be used before the expiry date. Out of date tars may be less effective due to evaporation of volatile constituents. Increased toxicity is not likely to occur.

hazards/toxicity:
Tars contain various toxic, irritating and carcinogenic constituents. While handling coal tar, avoid contact with the skin and breathing of vapours. After accidental contact with the skin, wash with water and soap.

● Dithranol

anthralin, dioxyanthranol, 1,8 dihydroxy 9 anthron

description:
Dithranol is a yellow to yellowish-brown crystalline powder.

package:
Dithranol should be packed in airtight containers which provide protection against exposure to light.

storage:
Dithranol should preferably be kept cool. It should be used before the expiry date. Out of date dithranol is less effective. It is not known whether out of date dithranol is more toxic or not. Degraded dithranol shows a discolouration to purple-brown or black.

hazards/toxicity:
Dithranol is a powerful irritant. While handling dithranol, avoid contact with the skin and the eyes. In the case of accidental contact with dithranol rinse the skin or the eyes immediately with water.

● Gentianviolet

CI basic violet 3, colour index no 42555, crystalviolet, hexamethylpararosaniline chloride, methylrosaniline chloride, pyoctaninum caeruleum.

description:
Gentianviolet consists of crystals with a greenish-bronze colour. It is odourless or almost odourless.

qualities/varieties:
Gentianviolet consists of a mixture of triphenylmethane dyes. Various qualities are marketed that contain different homologues. Preferably the pure dye is used for the preparation of gentianviolet solution.

package:
Gentianviolet should be packed in airtight containers.

storage:
Gentianviolet does not require special storage conditions.
It is quite stable and may be used as long as it has a good appearance and colour.

hazards/toxicity:
Undissolved crystals or solutions with a strength of more than 1% may be irritating on the skin and may cause necrotic skin reactions. After accidental contact with the skin or the eyes rinse immediately with a lot of water. After contact with the eyes, rinse immediately with a lot of water and get medical advice.
Gentianviolet is a very staining substance.
Gentianviolet has been suspected of being carcinogenic, but this has not been proven.
After ingestion of gentianviolet local corrosion of the gullet and stomach may result. Get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

● Glycerin

glycerol

description:
Glycerin is a clear syrupy liquid that should be almost colourless and almost odourless.

qualities/varieties:
Glycerin is miscible with water. Some pharmacopoeias also include a 85% glycerin. For the preparation of calamine lotion, both qualities may be used.

density:
pure glycerin: 1 ml = 1.26 g 1 g = 0.79 ml.
85% glycerin: 1 ml = 1.22 g 1 g = 0.82 ml.

package:
Glycerin should be packed in airtight containers.

storage:
Glycerin should preferably be kept at room temperatures.
At low temperatures it may solidify. To melt it, warm gently to a temperature slightly above 20°C.
Glycerin should preferably be used before the expiry date, but it can be used beyond, as long as the appearance remains satisfactory.

hazards/toxicity:
Glycerin is relatively non toxic. After accidental ingestion of very large doses headache, nausea and thirst may develop.

● Hydrocortisone acetate

description:
Hydrocortisone acetate consists of a white or almost white powder.

package:
Hydrocortisone acetate should be packed in airtight containers which provide protection against exposure to light.

storage:
Hydrocortisone acetate does not require special storage conditions. It should be protected from light. Hydrocortisone acetate should preferably be used before the expiry date mentioned on the package. Out of date hydrocortisone acetate may be less effective.

hazards/toxicity:
After accidental ingestion get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha.

● Industrial methylated spirit
alcohol

description:
Industrial methylated spirit is a colourless liquid with a characteristic odour.

qualities/varieties:
Methylated spirit is alcohol that has been made unsuitable for human consumption through the addition of methanol. Types of methylated spirit marketed in Great Britain are:
- Industrial methylated spirit: ethanol with 5% wood naphtha;
- Industrial methylated spirit pyridinised: ethanol with 5% wood naphtha and some pyridine;
- Industrial methylated spirit Q grade: ethanol with 5% methanol and quassia alkaloids;
- Power methylated spirit: ethanol with wood naphtha, benzene and pyridine;
- Mineralised methylated spirit: ethanol with wood naphtha, mineral naphtha, pyridine and methylviolet.

Methylated spirits containing pyridine can be recognised by their smell. Mineralised methylated spirit can be recognised by its blue colour. Household spirit is usually of the mineralised methylated spirit type. It can also be recognised by the fact that it produces an opaque solution upon mixing with water.
Spirits containing pyridine or benzene should not be used for dermatological preparations. Normal industrial methylated spirit is most suitable. For the preparation of iodine tincture, however, a special quality should be used, that is free from acetone and other ketones.
Spirit is methylated because of tax reasons. If a government is willing to exempt pure pharmaceutical ethanol from taxes, this ethanol can also be used.
The alcohol content of the spirit is of course very important. 95% industrial methylated spirit, also known as 66 OP, is suitable. If the spirit has to be diluted, weaker spirits may be used,

but the amount needed has to be calculated carefully.
This calculation can be done with the following formula:
amount to be diluted with water to 100 ml = 100 x dilution wanted/dilution available. An example: you want to prepare a 70% spirit. Your industrial methylated spirit has a strength of 90%. You should dilute 100 x 70/90 ml = 78 ml of the spirit with water to 100 ml to obtain the right dilution.

package:
Industrial methylated spirit should be packed in an airtight container.

storage:
Industrial methylated spirit should be kept as cool as possible, preferably below 15°C.

hazards/toxicity:
Industrial methylated spirit is inflammable. Ethanol is toxic if ingested in large quantities. The methanol used to make the spirit unsuitable for human consumption is even more toxic. If the spirit is ingested, get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha and give a 5% sodium bicarbonate solution in water orally.

● Iodine

description:
Iodine consists of greyish-violet to bluish-black plates or crystals with a metallic shine and an irritant odour. Iodine is volatile at 20°C.

package:
Iodine should be packed in airtight containers made of glass or earthenware.

storage:
Iodine should preferably be kept cool. It may evaporate if the container is not well closed.

hazards/toxicity:
Iodine forms strongly irritant substances with acetones and other ketones. Iodine is irritant to the skin and the eyes. While handling iodine, avoid contact with the skin and the eyes. Iodine is strongly irritant and toxic when ingested. After accidental ingestion get medical advice. While waiting for a doctor, give milk and starch first and then induce vomiting with syrup of ipecacuanha. If starch is not available, sodium thiosulphate may be used.

● Lanette wax

cera emulsificans, emulsifying wax

description:
Lanette wax is an almost white or pale yellow waxy solid or flakes. It has a faint characteristic odour.

qualities/varieties:
Lanette wax is both a trade name for a number of mixtures of fatty alcohols and other constituents, and a non official name for some of these mixtures. Emulsifying wax is the name used in the British Pharmacopoeia for a mixture of 90% cetostearyl alcohol and 10% sodium lauryl sulphate. This is equivalent to lanette wax SX, a branded product. The British Pharmacopoeia also gives the preparation method. Another mixture commonly used consists of cetostearyl alcohol 90% and sodium cetostearyl sulphate 10%. This is official in the Belgium Pharmacopoeia; the German Pharmacopoeia has a similar preparation, and it is marketed as Lanette wax N.
Lanette wax SX and other mixtures of fatty alcohols with sulphonated fatty alcohols are

widely used in creams. All those similar mixtures are suitable for use in creams, but lanette wax SX gives the most stable cream, so this is preferred. The non official name lanette wax is used in this formulary to prevent the confusion between emulsifying ointment and emulsifying wax.

package:
Lanette waxes usually are stable and do not require special package materials. A particular product, however, can require a special package because it is sensitive to light or to oxygen from the air. Therefore, all those products should be stored in airtight containers, which provide adequate protection against exposure to light, unless otherwise indicated in the specifications of a particular product.

storage:
Lanette wax should preferably be kept below 25°. It may melt at higher temperatures and form a solid mass upon resolidification. Lanette wax should preferably be used before the expiry date. Out of date lanette wax however may be used as long as it has a satisfactory appearance and smell.

● Lindane

gammabenzene hexachloride, gamma BHC, gamma HCH, gamma hexachlorocyclohexane, gammexane.

description:
Lindane is a white crystalline powder which may have a slight odour.

package:
Lindane should be packed in airtight containers which provide adequate protection against exposure to light.

storage:
Lindane should be protected from light, otherwise it does not require any special storage conditions. Lindane is best used before the expiry date. Out of date lindane may be less effective.

hazards/toxicity:
Lindane is a toxic substance with general stimulating effects on the nervous system. While handling lindane, avoid contact with the skin and the eyes. After accidental ingestion restlessness, muscle spasms and seizures may develop. Get medical advice. While waiting for a doctor, induce vomiting with syrup of ipecacuanha as soon as possible. Diazepam injections may be needed to treat seizures. Otherwise treatment is supportive and includes assistance of respiration.
Lindane is harmful for the environment. Discarded lindane should be treated as chemical waste (chlorinated pesticides).

● Liquid paraffin

liquid petrolatum, oleum vaselini, vaselinum liquidum, white mineral oil.

description:
Liquid paraffin is a clear oily liquid. It is colourless and odourless or almost odourless.

qualities/varieties:
Liquid paraffin is a complex mixture of liquid hydrocarbons. Its composition differs according to the source of the petroleum used for its preparation. Liquid paraffin designates in most pharmacopoeias the heavy quality. Both heavy and light liquid paraffin may be used in dermatological preparations. The heavy variety is preferred, because it gives more stable preparations.

density:
The density of liquid paraffin varies with variety and composition. Calculations should preferably be based upon the exact density given in the product specifications.
Heavy variety: 1 ml = 0.83 - 0.89 g 1 g = 1.12 - 1.20 ml
Light variety: 1 ml = 0.82 - 0.88 g 1 g = 1.13 - 1.22 ml

package:
Liquid paraffin should be packed in airtight containers which provide adequate protection against exposure to light.

storage:
Liquid paraffin should be protected from light, otherwise no special storage conditions are required. Liquid paraffin is stable and may be used as long as it has a good appearance and smell.

● Liquified phenol
phenol aqueux, phenol liquefactum.

description:
Liquefied phenol is a colourless liquid with a characteristic odour. It may have a slight pink colour.

qualities/varieties:
Liquified phenol is a solution of water in phenol. It is used in various strengths, ranging from 77% to 90%. These are all suitable for use in the preparation of calamine lotion.

density:
1 ml = 1.05 g 1 g = 0.95 ml

package:
Liquefied phenol should be packed in airtight containers which provide adequate protection against exposure to light.

storage:
Liquefied phenol should preferably be kept cool.
It should be protected from light.
Degraded phenol has a pink colour. Slightly pink coloured phenol may still be used. Degraded phenol is less effective or ineffective.

hazards/toxicity:
Phenol is corrosive. Phenol itself and strong solutions (10% and higher) are irritant on the skin and the eyes and may cause chemical burns. While handling phenol, avoid contact with the skin and the eyes. After accidental contact remove contaminated clothes and wash the skin with a lot of water. After contact with the eyes wash immediately with a lot of water.
Phenol causes local corrosion with intense pain, nausea and vomiting after ingestion. These effects are followed by depression of the central nervous system, death usually results from respiratory failure. Doses of more than 1 gram may be fatal.
After accidental ingestion get medical advice. Empty the stomach as soon as possible, preferably with gastric lavage. This should be done carefully to prevent causing even more damage to the stomach and gullet. Give 50 ml of castor oil, or bring castor oil in the stomach to slow down absorption. Treatment otherwise is supportive: keep the patient warm, treat acidosis and assist respiration.
Phenol is absorbed through the skin.
Chronic exposure to phenol and other phenolic compounds may result in a chronic phenol intoxication. Weight loss, loss of appetite, dark urine and pain in the limbs are the most common symptoms of chronic phenol poisoning. Patients usually recover if exposure to phenolic compounds is stopped.

● Methylparaben

methyl hydroxy benzoate, methylis oxybenzoas, methyl parahydroxy benzoate, MOB.

description:

Methylparaben consists of a fine white crystalline powder or colourless crystals. It may have a slight odour.

package:

The packaging materials should protect methylparaben from exposure to light.

storage:

Methylparaben should be protected from light, otherwise no special storage conditions are required. Methylparaben should preferably be used before the expiry date. Out of date methylparaben may be less effective.

hazards/toxicity:

After accidental ingestion induce vomiting with syrup of ipecacuanha.

● Para aminobenzoic acid

aminobenzoic acid, PABA, pabacide, vitamin H'.

description:

Para aminobenzoic acid consists of white to slightly yellow crystals or a crystalline powder. It may have a slight odour.

package:

Para aminobenzoic acid should be packed in airtight containers which provide adequate protection against exposure to light.

storage:

Para aminobenzoic acid should be protected from light and preferably be kept cool. It should preferably be used before the expiry date. Out of date para aminobenzoic acid may be less effective.

hazards/toxicity:

Para aminobenzoic acid stains clothes and the skin.
Contact dermatitis may develop, avoid contact with the skin and the eyes while handling para aminobenzoic acid.
After accidental ingestion induce vomiting with syrup of ipecacuanha.

● Petrolatum

paraffinum molle, petroleum jelly, soft paraffin, vaseline.

description:

Petrolatum is a white to pale yellow translucent unctuous mass. It is almost odourless.

qualities/varieties:

Petrolatum is a complex mixture of solid and liquid hydrocarbons. Its exact composition varies according to the source and manufacturer. "Natural" petrolatum has a yellow colour. It contains various constituents that may cause sensitization reactions although such reactions are rare. In white petrolatum these constituents have been degraded with a bleaching agent. Inferior qualities of white petrolatum may contain residues of the bleaching agents used. These may cause skin irritation. Both qualities may be used in dermatological preparations. Vaseline is a trade mark in some countries, including Great Britain.

package:
Petrolatum should be packed in a container which provides adequate protection against exposure to light.

storage:
Petrolatum should be protected from light.
It should preferably be kept cool. At temperatures of 25°C and above separation of oil may occur. Petrolatum should be homogenised before dispensing or use.
Petrolatum is stable and may be used as long as its appearance remains satisfactory.

● Phenol

carbolic acid, hydroxybenzene.

description:
Phenol consists of colourless crystals or a crystalline mass. Upon storage it becomes pink. It has a characteristic odour.

package:
Phenol should be packed in airtight containers which provide adequate protection against exposure to light.

storage:
Phenol should preferably be kept cool. At higher temperatures it may melt. It should be protected from light.
Degraded phenol has a pink colour. Slightly pink coloured phenol may still be used. Degraded phenol is less effective or ineffective.

hazards/toxicity:
Phenol is corrosive. Phenol itself and strong solutions (10% and higher) are irritant to the skin and the eyes and may cause chemical burns. While handling phenol, avoid contact with the skin and the eyes. After accidental contact remove contaminated clothes and wash the skin with a lot of water. After contact with the eyes wash immediately with a lot of water.
Phenol causes local corrosion with intense pain, nausea and vomiting after ingestion. These effects are followed by depression of the central nervous system, death usually results from respiratory failure. Doses of more than 1 gram may be fatal.
After accidental ingestion get medical advice. Empty the stomach as soon as possible, preferably with gastric lavage. This should be done carefully to prevent causing even more damage to the stomach and gullet. Give 50 ml of castor oil, or bring castor oil in the stomach to slow down absorption. Treatment otherwise is supportive: keep the patient warm, treat acidosis and assist respiration.
Phenol is absorbed through the skin.
Chronic exposure to phenol and other phenolic compounds may result in a chronic phenol intoxication. Weight loss, loss of appetite, dark urine and pain in the limbs are the most common symptoms of chronic phenol poisoning. Patients usually recover if exposure to phenolic compounds is stopped.

● Polysorbate 80

polyoxyethylene 20 sorbitan mono-oleate, sorbimacrogol oleate 300.

description:
Polysorbate 80 is a clear brownish-yellow oily liquid with a faint characteristic odour.

package:
Polysorbate 80 should be packed in airtight containers which provide adequate protection against exposure to light.

storage:
Polysorbate 80 should be protected from light, otherwise no special storage conditions are required. It may be used as long as its appearance and smell remain satisfactory.

● Potassium iodide
kalium iodidum

description:
Potassium iodide consists of transparent or somewhat opaque crystals or a white powder. It is odourless and colourless.

package:
Potassium iodide should be packed in airtight containers which provide adequate protection against exposure to light.

storage:
Potassium iodide should be protected from exposure to light, otherwise no special storage conditions are required. Iodide may be released, this results in a yellow to brown discolouration. Discoloured potassium iodide may still be used for the preparation of iodine solutions for external use, but not for systemic preparations.

hazards/intoxications:
Potassium iodide is readily absorbed from the stomach after ingestion. After accidental ingestion get medical advice. While waiting for a doctor induce vomiting as soon as possible with syrup of ipecacuanha.

● Potassium permanganate
kalium hypermanganicum

description:
Potassium permanganate consists of dark purple to black crystals. It is odourless.

package:
Potassium permanganate should be stored in airtight containers which provide adequate protection against exposure to light. These should not be made of, or contain, organic materials such as paper or cork.

storage:
Potassium permanganate should be protected from light, otherwise no special storage conditions are required. It should preferably be used before the expiry date. Partially degraded potassium permanganate shows a brown discolouration. The degradation of potassium permanganate in solutions is increased by the degradation products. Degraded potassium permanganate is not effective. Out of date potassium permanganate may still be used, but it dissolves even more slowly than the original material. It may be used, but only if total dissolution can be guaranteed. This means that the solution should be filtered. In the presence of organic materials potassium permanganate is degraded rapidly. Therefore, the solution should never be filtered over organic materials such as cotton wool or paper. A glass filter is suitable.
The correct strength of a solution, prepared with partly degraded potassium permanganate, can only be determined on the colour. Solutions prepared with out of date potassium permanganate will contain degradation products, which cause a brownish colour through the purple colour, and will be less stable.

hazards/toxicity:

Potassium permanganate forms explosive mixtures with some organic substances. It is used for the production of firework and explosives.
Potassium permanganate crystals and solutions are very irritating and may cause chemical burns. While handling potassium permanganate, avoid contact with the skin and the eyes. After accidental contact with the skin remove contaminated clothes and rinse with a lot of water. After accidental contact with the eyes, rinse immediately with a lot of water. A sodium thiosulphate solution may be of help to inactivate potassium permanganate.
After accidental ingestion nausea and vomiting result. The liver and kidneys may get damaged, as well as the cardiovascular system. The fatal dose is assumed to be approximately 10 grams. Death may occur up to one month after intoxication.
After accidental ingestion get medical advice. While waiting for a doctor, give milk immediately to slow down absorption. A sodium thiosulphate solution may be useful to inactivate the permanganate if given immediately. Treatment otherwise is supportive and includes keeping the patient warm and assisting respiration.
Potassium permanganate is harmful for the environment. Discarded potassium permanganate should be treated as chemical waste (heavy metals).

● Salicylic acid

2-hydroxy benzoic acid, acido ortoxicobenzoico.

description:

Salicylic acid consists of colourless feathery crystals or a white crystalline powder. It is odourless, but dust particles irritate the nose.

qualities/varieties:

Salicylic acid is marketed in varying particle sizes. For use in dermatological preparations a particle size of about 90 µm is preferred. If a larger particle size is used, this should be grounded and preferably sieved before being incorporated in dermatological preparations. The exception to this rule is salicylic acid solution. All particle sizes are suitable for the preparation of this solution.

package:

Salicylic acid should be packed in airtight containers.

storage:

Salicylic acid requires no special storage conditions. Salicylic acid should preferably be used before the expiry date, but out of date salicylic acid may be used as long as the appearance and smell of the product remain satisfactory. The particle size of out of date salicylic acid may have changed. Therefore, out of date salicylic acid should always be sieved and, if necessary, grounded before being used.

hazards/toxicity:

Avoid inhaling salicylic acid dust, this is irritating.
Salicylic acid is moderately toxic. After ingestion of large amounts of salicylic acid, induce vomiting with syrup of ipecacuanha. Consult a doctor if very large amounts of salicylic acid are ingested.

● Silver nitrate

argenti nitras, nitrato de plata

description:

Silver nitrate consists of colourless crystals or a white crystalline powder. It is odourless.

package:
Silver nitrate should be packed in airtight, non metallic containers which provide adequate protection against exposure to light.

storage:
Silver nitrate should be protected from light, otherwise no special storage conditions are required. Degraded silver nitrate is less effective or ineffective. Degraded silver nitrate shows a discolouration to grey or greyish black. Silver nitrate with a slightly greyish colour may still be used. Stronger coloured silver nitrate should be discarded.

hazards/toxicity:
Silver nitrate crystals and strong solutions are caustic to the skin and the eyes. While handling silver nitrate, avoid contact with the skin and the eyes. After accidental contact remove contaminated clothes and rinse with a lot of water. Sodium thiosulphate solution may be used to inactivate silver nitrate.
After accidental ingestion of silver nitrate or silver nitrate solutions get medical advice. While waiting for a doctor, give a sodium chloride solution (household salt, about 1%) immediately and repeatedly. To empty the stomach induce vomiting with syrup of ipecacuanha. If available, gastric lavage is preferred. Give sodium sulphate as a purgative. If an analgesic is needed to treat the pain, paracetamol is preferred over aspirin.
Silver nitrate is harmful for the environment. Discarded silver nitrate should be treated as chemical waste (heavy metals).

● Sodium iodide
natrium iodidum

description:
Sodium iodide consists of transparent or somewhat opaque crystals or a white powder. It is odourless and colourless.

package:
Sodium iodide should be packed in airtight containers, which provide adequate protection against exposure to light.

storage:
Sodium iodide should be protected from exposure to light, otherwise no special storage conditions are required. Iodide may be released, this results in a yellow to brown discolouration. Discoloured sodium iodide may still be used for the preparation of iodine solutions for external use, but not for systemic preparations.

hazards/intoxications:
Sodium iodide is readily absorbed from the stomach after ingestion. After accidental ingestion induce vomiting as soon as possible with syrup of ipecacuanha. Get medical advice.

● Sodium thiosulphate
sodium hyposulphite

description:
Sodium thiosulphate consists of colourless crystals or a crystalline powder. It is almost odourless.

qualities/varieties:
Apart from pharmaceutical qualities, various technical qualities are marketed. Sodium thiosulphate is for example used as a fixation agent in photography. Such technical qualities may be used for the preparation of sodium thiosulphate solutions, provided they do not

contain any technical additives. If technical qualities are used, take care to prevent mix-ups with sodium thiosulphate of parenteral quality used as an antidote.

package:
Sodium thiosulphate should be packed in airtight containers.

storage:
Sodium thiosulphate does not require special storage conditions. It should preferably be used before the expiry date. Out of date sodium thiosulphate may be less effective.

● Sulphur

description:
Precipitated sulphur is a pale yellow, greyish-yellow or greenish-yellow, amorphous or microcrystalline powder, that should be odourless and tasteless.

qualities/varieties:
Different forms of sulphur are known in pharmacy:
- Precipitated sulphur (milk of sulphur, lac sulphuris) is a fine powder free from grittiness;
- Sublimed sulphur (flour of sulphur) is a gritty powder. Sublimed sulphur has, in contrast to precipitated sulphur, a characteristic odour;
- Washed sulphur is a special quality of sublimed sulphur. It is a fine, odourless, crystalline powder.

Because of its fine particle size, precipitated sulphur is most effective in dermatological preparations. If this is not available, washed sulphur can be used. Sublimed sulphur is less effective and should only be used if no precipitated or washed sulphur can be obtained.

package:
Sulphur does not require a special package.

storage:
Sulphur does not require special storage conditions. The risks associated with the use of out of date sulphur are considered low. Precipitated and washed sulphur should be odourless.

hazards/toxicity:
Sulphur has a low general toxicity. It can be used as an ingredient for fireworks and explosives, but pure sulphur is not explosive.

● Trisodium citrate
natrii citras, sodium citrate

description:
Trisodium citrate consists of colourless crystals or a white crystalline powder. It is odourless. It is slightly deliquescent in moist air and slightly efflorescent in warm dry air.

qualities/varieties:
Trisodium citrate dihydrate is recommended for use in oral rehydration solutions by the WHO, because of its wide availability. This quality is adequate for use in calamine lotion. The anhydrate may also be used, no correction is needed in this case. If other hydrates are used, correct for the difference in molecular weight.

package:
Trisodium citrate should be packed in airtight containers.

storage:
No special storage conditions are required. Trisodium citrate should preferably be used before the expiry date. Out of date trisodium citrate may be less effective. This may be used for the preparation of calamine lotion, as long as the resulting lotion can be easily poured out of a medicine bottle.

● Urea

carbamide

description:
Urea consists of colourless crystals or pellets, or a white crystalline powder. It is almost odourless.

package:
Urea should be packed in airtight containers.

storage:
Urea should preferably be kept cool. Degraded urea has the smell of ammonia. It may still be used but it may be less effective.

hazards/toxicity:
Urea is relatively non toxic. After accidental ingestion nausea and vomiting may occur.

● Vegetable oil

description:
Vegetable oils are oily liquids. Most of them have some characteristic odour. Their colours range from colourless to yellow or brown.

qualities/varieties:
A great number of vegetable oils are used worldwide in foods. Their characteristics differ according to the plant source and manufacturing process. All vegetable oils suitable for human consumption may be used for the preparation of dermatologicals, except for oils with a high sensitization potential, such as sesame oil. Various native oils may also have a high sensitization potential. If you see many sensitization reactions resulting from the use of zinc oil, switch to some other vegetable oil.

package:
Vegetable oils should be packed in airtight bottles which provide adequate protection against exposure to light.

storage:
Vegetable oils should be protected from light, otherwise no special storage conditions are required. Native oils do not generally carry expiry dates. They should be judged upon their smell and appearance. Older oils, especially if they have been exposed to light and oxygen from the air, have a high acid content. This results in poor stability of the zinc oil prepared with them. If you have problems with the stability of zinc oil, switch to other oils or recently manufactured oils.

● Water

description:
water is a clear colourless and odourless liquid.

qualities/varieties:
Water may be obtained from various sources, such as rain water, underground water, surface water and tap water. The water used for dermatological preparations should be of at least potable quality. The water for the preparation of dermatologicals should always be freshly boiled and cooled. This means it should be heated until it boils and cooled, and that it should be used within one day.

density:
1g = 1 ml.

storage:
Water should not be kept as it will readily get contaminated with micro-organisms. Water that should be kept has to be preserved, for example by chlorination.

● Zinc oxide
blanc de zinc, flores de zinc, zinc white

description:
Zinc oxide is a very fine, white or slightly yellowish-white powder. It is odourless. It feels soft if rubbed between two fingers.

qualities/varieties:
Zinc oxide is widely used as a pigment. Technical qualities such as zinc white may contains various technical additives. In addition, they may have other particle size characteristics. It is therefore best to use a pharmaceutical quality.

package:
Zinc oxide should be stored in airtight containers.

storage:
Zinc oxide does not require special storage conditions. It has a practically indefinite shelf life.

hazards/toxicity:
Inhalation of dust particles should be avoided, but zinc oxide does not cause asbestosis.

7 Vocabulary

accurate correct, making no mistakes

adjacent next to, neighbouring

adverse reactions unwanted reactions

aggressive said of a substance that attacks many materials, including human skin

antiseptic a substance used to kill micro-organisms on the human skin

autoclave to sterilize by boiling under pressure

balance an instrument for weighing

batch a group of things made at the same time

batch number a specific number given to each product of the same batch

calibrate to correct an instrument so that it may be used for precise measurements

carcinogenic a substance that can cause cancer

container a container is anything, such as a box, bag, tin or pot, into which things can be put.

contamination dirtiness or infection caused by contact

corrosive said of a substance that attacks certain materials

cream a soft, wet mixture of fats and water

degradation break down, decomposition

disinfectant a substance used to kill micro-organisms

dispense to sell or hand out medicines

dissolve to cause some solid matter to disappear in a liquid

dose the amount of medicine that should be taken by or given to a patient

emollient a preparation that hydrates the skin and makes it softer

emulsion a homogeneous mixture of fats and water

equivalent the same as, comparable to

expiry date date after which the quality of a product can no longer be guaranteed

extemporaneous extemporaneous preparations are dispensed immediately after production

external use use on the skin

forceps tweezers, small instrument to pick up small things

formula a list of ingredients and the amounts to be taken

fungistatic a substance that is able to slow down the growth of fungi

gradually part by part, not at once

hazard danger

homogeneous completely mixed

hydrate to wet the skin through and through

hygiene general cleanliness

inferior of a lesser quality

inhomogeneous not completely mixed, partly separated

intoxication poisoning

irritation pain or burning sensation due to contact with a substance. Irritation is due to slight damage. Irritation may develop in everybody (cf sensitization)

lactation breast feeding

level a certain height, resembling a certain amount

manufacturing process a series of actions by which a product is made

measure an instrument for measurements of volume

measurement the determination of length, weight, volume etc. of something

micro-organisms tiny germs that can only be seen with a microscope and that can cause infections. Bacteria, fungi and yeasts are micro-organisms

mixing to put different things together so that they form one substance

mixing efficiency resulting in a good quality of mixing

moisturizer a preparation that hydrates the skin

monograph a piece of text about one particular preparation or material

mutagenic a substance that causes damage to the genes. Such substances may also be carcinogenic and teratogenic

mycotic fungal

ointment a soft mixture consisting mainly of fats

out of date a product is out of date if the expiry date has been passed

paste a soft mixture of a powder and a liquid or a semisolid that is easily spread

photosensitization sensitization due to the combination of a drug and sunlight. If exposure to sunlight is avoided, sensitization will not occur

phototoxicity toxic reaction due to the combination of a drug and sunlight. If exposure to sunlight is avoided, toxic reactions will not occur

pictogram a drawing or painting used to give information

pipette an instrument for measurement of small volumes

premises buildings

preservative a substance able to prevent the growth of micro-organisms. It is added to a number of preparations to prevent microbial spoilage

quality how well something has been done

quantity the amount of material

raw material starting material, the natural substance from which a product is made

resistance if microbes or parasites are no longer killed by a medicine they are said to be resistant

S.I. unit system a set of units used internationally. It comprises for example the meter and the kilogram

semisolid a soft material, halfway between a solid and a liquid. It cannot be poured like a liquid but it isn't hard like a solid either.

sensitization reaction of the body to repeated contact with a substance, with pain, redness or itch. Sensitization is not due to damage. It develops in a few persons only (cf irritation)

separation two things going away from each other. Also the inverse of mixing

shelf life the period a certain preparation can be kept in store

side effects unwanted effects resulting from the use of a medicine

sieve an object with a wire network stretched across the bottom of a frame. It is used to separate small objects, which fall through, from large objects, which stay on the frame

solubility to what extend a specific solid can be dissolved in a specific liquid

spoil to waste

sterilization to make free from living micro-organisms, usually by boiling or heating

stock a quantity of goods kept in store

suction bulb a rubber bulb used to draw liquid into a pipette

superficial only concerns the outer part of the skin

synonyms different words with the same meaning

systemic of internal parts of the body

tare (said of a balance) set to zero or brought into balance

teratogenic harmful for the unborn child

toxic poisonous, a substance which causes sickness

triturate to rub between the wall of a mortar and a pestle

ultraviolet rays invisible radiation, part of the radiation spectrum of the sun.

unit an amount or quantity taken as a standard of measurement. In production unit: production facility, production centre.

vessel a container, usually for liquids

volume the measure of space taken up by something

waxed paper paper with a layer of wax on it, used to weigh fatty substances

weigh to find the weight of a certain amount

weight the heaviness of something

weight a piece of metal with a standard heaviness

8 Synonyms

Acido ortoxibenzoico
  salicylic acid
Alcohol
  industrial methylated spirit
Aluminium magnesium silicate
  magnesium aluminium silicate
  saponite
Aminobenzoic acid
  para aminobenzoic acid
Anthralin
  dithranol
Anthralin cream
  dithranol cream
Anthralin paste
  dithranol paste
Argenti nitras
  silver nitrate
Ascorbic acid
  vitamin C
Bentonite
  mineral soap
  soap clay
  wilkinite
Benzoic and salicylic acid cream
  whitfield's cream
Benzoic and salicylic acid ointment
  whitfield's ointment
Benzylbenzoate application
  benzylbenzoate emulsion
Benzylbenzoate lotion
  benzylbenzoate emulsion
Blanc de zinc
  zinc oxide
Carbamide
  urea
Carbolic acid
  phenol
Cera emulsificans
  lanette wax
CI basic violet 3
  gentianviolet
Coal tar
  pix carbonis
  pix lithantracis
Colour index no 42555
  gentianviolet
Crystalviolet
  gentianviolet
Crystalviolet solution
  gentianviolet solution
1,8 Dihydroxy 9 anthron
  dithranol
Dioxyanthranol
  dithranol
Dithranol
  1,8 dihydroxy 9 anthron
  anthralin
  dioxyanthranol
Dithranol cream
  anthralin cream
Dithranol paste
  anthralin paste
Emulsifying wax
  lanette wax
Flores de zinc
  zinc oxide
Flour of sulphur
  sublimed sulphur
Gamma BHC
  lindane
Gamma HCH
  lindane
Gamma hexachlorocyclohexane
  lindane
Gammabenzene hexachloride
  lindane
Gammexane
  indane
Gammexane cream
  lindane cream
Gentianviolet
  CI basic violet 3
  colour index no 42555
  crystalviolet
  hexamethylpararosaniline chloride
  methylrosaniline chloride
  pyoctaninum caeruleum
Gentianviolet solution
  crystalviolet solution
  methylrosaniline chloride solution
Glycerin
  glycerol

Glycerol
glycerin
Hexachlorocyclohexane cream
lindane cream
Hexamethylpararosaniline chloride
gentianviolet
Hydrocortisone acetate cream
hydrocortisone cream
Hydrocortisone acetate ointment
hydrocortisone ointment
Hydrocortisone cream
hydrocortisone acetate cream
Hydrocortisone ointment
hydrocortisone acetate ointment
Hydroxybenzene
phenol
2-Hydroxybenzoic acid
salicylic acid
Industrial methylated spirit
alcohol
Kalium hypermanganicum
potassium permanganate
Lac sulphuris
precipitated sulphur
Lanette wax
cera emulsificans
emulsifying wax
Lindane
gamma benzene hexachloride
gamma BHC
gamma HCH
gamma hexachlorocyclohexane
gammexane
Lindane cream
gammexane cream
hexachlorocyclohexane cream
Liquid paraffin
liquid petrolatum
oleum vaselini
vaselinum liquidum
white mineral oil
Liquid petrolatum
iquid paraffin
Liquified phenol
phenol aqueux
phenol liquefactum
Magnesium aluminium silicate
aluminium magnesium silicate
Methyl hydroxy benzoate
methylparaben
Methyl parahydroxy benzoate
methylparaben
Methylis oxybenzoas
methylparaben
Methylparaben
methyl hydroxy benzoate
methylis oxybenzoas
methyl parahydroxy benzoate
MOB
Methylrosaniline chloride
gentianviolet
Methylrosaniline chloride solution
gentianviolet solution
Milk of sulphur
precipitated sulphur
Mineral soap
bentonite
MOB
methylparaben
Natricum nitrosum
sodium nitrite
Natrii citras
trisodium citrate
Nitrato de plata
silver nitrate
Oleum vaselini
liquid paraffin
PABA
para aminobenzoic acid
Pabacide
para aminobenzoic acid
Para aminobenzoic acid
aminobenzoic acid
PABA
pabacide
vitamin H'
Para aminobenzoic acid cream
PABA cream
Para aminobenzoic acid solution
PABA solution
para aminobenzoic acid lotion
Paraffinum molle
petrolatum
Petrolatum
paraffinum molle
petroleum jelly
soft paraffin
vaseline
Petroleum jelly
petrolatum
Phenol
carbolic acid
hydroxybenzene
Phenol aqueux
liquified phenol
Phenol liquefactum
liquefied phenol
Pine tar
wood tar

Pix
  tar
Pix carbonis
  coal tar
Pix liquida
  wood tar
Pix lithantracis
  coal tar
Pix pini
  wood tar
Polyoxyethylene 20 sorbitan mono-oleate
  polysorbate 80
Polysorbate 80
  polyoxyethylene 20 sorbitan mono-oleate
  sorbimacrogol oleate 300
Potassium permanganate
  kalium hypermanganicum
Precipitated sulphur
  lac sulphuris
  milk of sulphur
Pyoctaninum caeruleum
  gentianviolet
Salicylic acid
  acido ortoxicobenzoico
  2-hydroxy benzoic acid
Saponite
  aluminium magnesium silicate
Silver nitrate
  argenti nitras
  nitrato de plata
Soap clay
  bentonite
Sodium citrate
  trisodium citrate
Sodium hyposulphite
  sodium thiosulphate
Sodium nitrite
  natricum nitrosum
Sodium thiosulphate
  sodium hyposulphite
Soft paraffin
  petrolatum
Sorbimacrogol oleate 300
  polysorbate 80
Stockholm tar
  wood tar
Sublimed sulphur
  flour of sulphur
Sulphur lotion
  sulphur/calamine lotion
Tar
  pix
Trisodium citrate
  natrii citras
  sodium citrate
Urea
  carbamide
Vaseline
  petrolatum
Vaselinum liquidum
  liquid paraffin
Vitamin C
  ascorbic acid
Vitamin H'
  para aminobenzoic acid
White mineral oil
  liquid paraffin
Whitfield's cream
  benzoic and salicylic acid cream
Whitfield's ointment
  benzoic and salicylic acid ointment
Wilkinite
  bentonite
Wood tar
  pine tar
  pix liquida
  pix pini
  stockholm tar
Zinc oil
  zinc oxide liniment
Zinc oxide
  blanc de zinc
  flores de zinc
  zinc white
Zinc oxide liniment
  zinc oil
Zinc oxide paste
  zinc paste
Zinc paste
  zinc oxide paste

Part II:

Backgrounds of choices, formulation and dispending

9 Introduction: dermatological preparations for the tropics

1 history of the project

Since the foundation of the Scienceshop for Medicine (Wetenschapswinkel voor Genees-middelen) questions have been asked by health workers in Third World countries. Many of these questions concerned storage and local preparation of pharmaceuticals. Reports on some of these topics have been published by the Scienceshop for Medicine, e.g. on small scale production of intravenous fluids (Van Dooren 1984). Because of the wide interest in local production, research has continued in this field.

The incidence of dermatological disorders in the Third World is very high. Prevalence rates have been reported to be as high as 80%, but a rate of 96% has been reported too (Porter 1977). Different numbers have been cited, depending on the definition of the prevalence rate used. In the Third World skin diseases form one of the main reasons for seeking medical advice. Nevertheless, little attention has been paid to the provision of adequate dermatological drugs for use in tropical Third World countries. At best some preparations developed for use in temperate climates are available. For use under tropical conditions dermatologicals should meet more stringent requirements, such as being stable at higher temperatures. Western preparations should not be used in tropical countries unless their suitability has been demonstrated. It was thus not so clear what preparations were suitable for both local production and use under tropical conditions. This problem was also recognised at the international workshop "dermatology in basic health services" , jointly organised by the German Foundation for International Development and the Scientific Secretariat of the 17th International Congress of Dermatology in Berlin May 1987. It was concluded at the workshop that there is an urgent need for national formularies meeting basic dermatological needs.

Therefore, we decided to try to prepare a formulary, with the intention of meeting basic dermatological needs of the majority of the population of tropical Third World countries, and focusing on local production.

2 Alma Ata and primary health care

At the international WHO/Unicef conference in Alma Ata in 1978 new goals and policies were formulated. The main goal formulated was "Health for all by the year 2000". The conference declaration defined health -which is optimal, physical, mental and social wellbeing- as a fundamental human right. Participation was considered of utmost importance, article 4 of the declaration stated "People have the right and duty to participate individually and collectively in the planning and implementation of their health care".

The primary health care (PHC) concept was developed as one of the main instruments for reaching the ambitious goal of health for all by the year 2000. Primary health care was defined in article 6 of the declaration as:

> "Primary health care is essential health care based on practical, scientifically sound and socially acceptable methods and technology made universally accessible to individuals and families through their full participation and at a cost that the community and country can afford to maintain at every stage of their development in the spirit of self reliance and self determination. It forms an integral part both of the countries' health system, of which it is the central function and main focus, and of the overall social and economic development of the community. It is the first level of contact of individuals, the family and com-

munity with the national health system, bringing health care as close as possible to where people live and work, and constitutes the first element of an continuing health care process".

In the next articles of the declaration the concept is worked out in more detail:
- PHC should reflect and evolve from the economic conditions and socio-cultural characteristics of the country and community;
- PHC should address the main health problems;
- PHC should include at least education, nutrition, water, maternal and child care, family planning, immunization and treatment of common diseases;
- PHC should involve related sectors;
- PHC requires and promotes maximum community and individual self reliance and participation in planning, organization, operation and control (declaration of Alma Ata, CONTACT, special series 1, april 1979).

3 essential drugs

In 1977 the first WHO essential drugs list was published. The purpose of the list was to extend the availability of the most essential drugs to those populations whose needs could not be met by the existing system by limiting the number of drugs available to those considered essential. Only drugs with proven effectiveness and safety and necessary for treatment of the main health problems should be available. Limited lists can be useful for promoting rational prescribing too (e.g. hospital formularies in the Netherlands).

As the differences between countries, or even regions, can be great the preparation of one uniform drugs list is not possible. Each country should therefore develop its own list, depending on needs, health care system, financial resources, and genetic, demographic and environmental factors.

Because situations may change in time and more information and new drugs may become available, there is a need to review any essential drugs list regularly. The WHO recommends to review the essential drugs lists at least once a year (WHO expert committee 1988).

To make sure choices are as objective as possible, they should be based on well formulated criteria. The WHO indicates some of the criteria to be used. Choices should be based on a benefit/risk ratio, as determined in controlled trials. Generic names should be used whenever feasible. Choices between therapeutically equivalent drugs can be based on benefit/cost ratios, stability, amount of information available, kinetic parameters and the possibility for local production of the drug. Quality must be guaranteed. The local situation should be carefully considered (e.g.prevalence of malnutrition, liver diseases).

Since 1979 The WHO specifies the pharmaceutical forms in the essential drugs lists. This is important as a drug consists of both active ingredient and vehicle. The route of administration and the vehicle used are main factors in determining price, effectiveness, stability and pharmacokinetics. If the essential drugs concept is ever to be effective, not only the number of active ingredients should be limited, but the number of preparations as well. In only a few cases, more forms should be available. This can be the case if one drug is used for various diseases. In many cases the WHO indicates the pharmaceutical form only vaguely. This may be the case if various forms are considered equivalent. The cheapest available preparation should then be taken.

Primary health care depends on local health workers. They are essential to get health services as close to the people as possible and to promote participation. These local health workers usually have little formal training. Facilities at village level are generally quite basic. It is therefore necessary to prepare a limited list of essential drugs suitable for use at this village level. This must be done at a national or regional level as it is impossible to prepare such a list internationally (WHO expert committee 1977, 1988).

4 local production of drugs

Local production may be important to increase the independence of Third World countries and to enhance self reliance, knowledge and experience, and participation (Raghoebar 1982; Melrose 1982; DeNever and Plaizier-Vercammen 1989). Local production may be cheaper. Local production can be implemented stepwise, starting with packaging and simple preparations. Some countries in the Third World have developed extensive national drugs industries, for example India and Brazil. Considering the local situation and resources, both human and financial, governments must decide whether, and to what extent, local production is feasible. Some factors and controversies to be considered are cost effectiveness, stability, dependence on the developed world and local infrastructure.

A thorough analysis of costs and profits of local production of drugs is difficult. Both costs and profits may be financial or non financial, short term or long term. Starting local production means investing (lots of) money, most probably hard foreign currency. But highly qualified work remains in the country and buying drugs will press on foreign currency reserves too. In the long run, dependence may become less and less. In some cases, particularly in the production of intravenous fluids and other solutions, local production is very cost effective as transport costs are a major part of the price of such drugs, and these preparations mainly involve locally available raw materials, such as water.

In general, unstable drugs should not come into contact with water. This means that stability and shelf life of preparations that contain water -as most dermatologicals do- is limited. The advantages of preparing these drugs at or near the place where they are needed is clear.

Dependence from the industrialized countries may persist even if drugs are locally produced. This may be the case if production technology remains in the hands of foreign, often transnational companies or their local subsidiaries. Another problem is the provision of raw materials. Most of these should be imported, particularly during the first stages of local production, and dependence in such cases may only be shifted from finished products to raw materials. Cooperation between developing countries is very important. Many of the raw materials needed for drug preparation are available from regional or other Third World producers. Dependence will not disappear from one day to another, but the problem can be tackled. Governments and others should address this problem. If no action is taken towards local production it will most certainly not develop.

Even ideal drugs are only effective and safe if used correctly. Good information is crucial. Information should be given in local languages and in pictograms too. Both written information and pictograms should take full account of the local situation and customs.
Information should thus be locally produced. Information is best given on the package; specially on primary package as this will remain close to the product. This is a strong argument for local packaging.

Quality assurance is crucial; this holds for locally produced and for imported drugs. National or regional quality control laboratories may play an important role. Good quality assurance may enhance acceptance of locally produced drugs. Quality assurance depends on preparation methods and organization as well. This aspect should be taken into account in the selection of preparations and preparation methods (WHO expert committee 1988).

5 basic needs

Drugs for Primary Health Care (PHC) should cover basic needs of the majority of the population. What are those basic needs in dermatology? Needs will differ from country to country and from region to region, but some characteristics of tropical Third World dermatology remain essentially constant. There are more differences comparing Third World countries with developed countries, than there are if various Third World countries are compared.

Two main contrasts are the contrasts tropical climate/temperate climate (tropical versus cosmopolitan diseases) (Manson-Bahr and Bell 1987) and the contrast Third World/developed world (infectious versus noninfectious diseases) (Porter 1977).

The contrast infectious diseases versus noninfectious diseases is characterised by the high incidence of infectious diseases in the Third World and the low incidence of these diseases in

the developed world. The incidence of noninfectious diseases is essentially constant throughout the world, although there are some regional variations (Porter 1977; Anderson and Maibach 1979). The incidence of infectious diseases depends mainly on three sorts of factors:

- individual factors, the most important of which are age, nutritional status and acquired immunity, and of cause personal hygiene. Sex, race and migration may be other factors. Children are far more vulnerable to infectious diseases than adults. As the population structure in most Third World countries is characterised by a relatively high proportion of children a higher incidence of infectious diseases in the Third World is to be expected.
- ecological factors: climatological factors such as humidity and temperature may influence the incidence of infectious diseases. Other ecological factors are the presence of water, swamps, woods, type of soil and many others.
- socioeconomic factors (development) are the most important factors determining incidence of infectious skin diseases. Housing conditions (overcrowding), sanitary conditions, water supply, preventive health care, nutrition and curative medicine are some factors. Of these curative health care is the least important. The pattern and incidence of infectious diseases in the Third World is similar to the situation in Europe as it was a century ago. It has changed in Europe due to housing, piped water supply, sewage, higher wages and education programs. Curative medicine played only a minor role. This is illustrated by the fact that the most rapid changes in the situation were seen before anti-infective treatment became available (Porter 1977; Melrose 1982).

Scabies, mycotic infections and pyoderma are the most important skin diseases in the Third World. Primary pyoderma is usually caused by *Staphylococcus aureus* or *Streptococcus pyogenes*. The former is more common in temperate zones, the latter is more prevalent in tropical regions and under poor hygienic circumstances. Streptococci are more dangerous than staphylococci (Taplin et al. 1973; Leyden and Kligman 1978).

The classification of diseases in tropical and cosmopolitan diseases is unsatisfactory. Usually three types of diseases are distinguished (Manson-Bahr 1987):

1. cosmopolitan diseases;
2. cosmopolitan diseases that have a different presentation or incidence in tropical regions;
3. genuine tropical diseases (limited to tropical regions).

The last group is very small. Most diseases generally called "tropical" are part of group 2. A good example is malaria. In the Netherlands this "tropical" disease was once endemic. Only in the late sixties of this century were the Netherlands considered to be free from malaria, this was even later than some countries in tropical regions.

The causes for differences in incidence or presentation happen to be the same factors influencing the high incidence of infectious diseases in Third World countries. In fact infectious diseases are a good example of group 2 diseases.

6 conclusions

The chapter on basic needs indicates strongly that drug treatment is neither the most appropriate, nor the most relevant way of improving the health status of the population. The underlying causes, especially socioeconomic factors, must be adequately addressed if real changes are to be obtained in Third World countries. But still, individuals need treatment for their diseases. Drug treatment should thus be part of an integrated approach to health care in tropical regions. Drugs for treatment of dermatological diseases are the main subject of this book.

Local production may play an important role, especially in the long run, in reducing cost and dependence, enhancing self reliance and reaching as many people as possible.

To make the best use of limited resources and to ban useless, dangerous and overpriced drugs, the essential drugs concept is crucial.

Primary Health Care is the best way to reach the majority of the population. We thus focus on preparing a limited list of effective dermatologicals that may be prescribed safely by village health workers and that can be prepared in the country itself. In addition we will also consider drugs for use in hospitals. This limited list may need local adaptation, but this is more likely to result in deletion of certain drugs than in addition of others.

7 criteria

The principles set out in this chapter are translated into the following selection criteria:

* need:
  The preparation must be effective for treatment of skin diseases that affect many people. There is no need for drug treatment if treatment is useless or if non-drug treatment is as good as, or better than, drug treatment.

* benefit/risk ratio:
  Effectiveness must be well documented, preferably with controlled clinical trials. The drug that has the fewest side effects should be taken. If misuse or abuse of a drug may result in major risks the use of that drug should be avoided. The tropical situation should be considered, not only the situation in western countries. Risks associated with the use of drugs in malnourished people or people with endemic diseases, for example endemic hepatitis, malaria or AIDS, should be carefully assessed.

* benefit/cost ratio:
  Benefits and costs should be carefully evaluated. Cost estimates should be based on treatment prices, not on unit prices. Transport costs should also be considered. Treatment cost estimates should include any additional costs, such as the bandages needed or hospital admissions. Also, non-financial costs and benefits should be taken into account.

* vehicle:
  Selection of drugs is incomplete if only active ingredients are considered. This holds for any drug, but especially for dermatologicals. These preparations should be washable, non occlusive and appropriate for use in the skin conditions concerned. They should be easy to pack and simple to apply, even under tropical conditions.

* stability:
  Raw materials and preparations must show good chemical, physical and microbiological stability under adverse storage conditions. If excessive chemical degradation or toxicity of the degradation products is expected with a specific ingredient this ingredient should be avoided.

* preparation:
  The formulation must be easy to prepare by personnel with little training. Preparation must be possible with only a limited number of simple utensils. Preparation methods should guarantee highest possible quality.

* raw materials:
  Raw materials must be cheap and easy to obtain from local or regional sources. They must be simple to process. Any hazardous material should be avoided (toxic, inflammable or explosive).

* package:
  Package should in general ensure integrity of the preparation and protection against external effects. For tropical use package should in addition be light, reusable, and it should protect the preparation against evaporation or adsorption of water, and excessive exposure to light.

No drug will meet all these standards. The best drugs should be chosen considering the local situation. This should preferably be done on a national or regional basis but it is possible to indicate some generally applicable drugs and to prepare a basic formulary for use in tropical countries. Still, these choices should be reconsidered by the local health authorities. In certain cases more than one suitable preparation is indicated. In these cases the choice should be based on the local situation.

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10 Dermatological therapy in tropical third world countries

1 Drugs for the treatment of infectious diseases

1.1 introduction

Infectious diseases are the main problem in tropical Third World countries (see chapter 9); among these, scabies, pyoderma and mycoses occur most. Generally, therapy can be both systemical and local, the choice being dependent on the type of disease.

Antiseptics are preparations for use on living material, the intention of use being a reduction in the number of micro-organisms on the treated material. In contrast, disinfectants are intended for use on non living material such as instruments. Antiseptics should be well tolerated and non toxic. The difference between antibiotics and antiseptics is less clear. Antibiotics are generally products from biological sources, active in small concentrations, with a specific mode of action against a small range of micro-organisms. The consequence is a risk for the development of resistance. Antiseptics are generally quite simple chemicals with an aspecific mode of action. This implicates less sensitization potential, less resistance and a broad spectrum of action, but greater toxicity too. Antiseptics are more adequate for topical treatment of simple dermatological infections, but they are not suitable for systemic use. The above definition does not apply to all antibiotics or antiseptics and is of limited value, but still useful.

1.2 bacterial diseases

Primary pyodermas are usually caused by either *Staphylococcus aureus* or *Streptococcus pyogenes*. Secondary pyodermas can be caused by many kinds of bacteria if a primary lesion is present. In secondary pyodermas both *Staphylococcus aureus* and *Streptococcus pyogenes* are frequently found.

In temperate zones and under good hygienic conditions *Staphylococcus aureus* is the main problem. This is a normal commensal on human skin. *Streptococcus pyogenes* is not so generally found on human skin and is not likely to be able to survive on healthy human skin. At higher temperatures, higher humidity or poorer hygienic circumstances, this is in fact the situation in tropical Third World countries, *Streptococcus* is more generally found in primary and secondary pyodermas (Taplin et al. 1973; Leyden and Kligman 1978). *Streptococcus* is the more dangerous of the two, generally causing deeper infections and in about 1% of all cases complications such as endocarditis and nefritis. Therefore some authors recommend treating every streptococcal pyoderma with systemic antibiotics. However, it has been shown that systemic treatment did not alter incidence nor seriousness of nefritis (Leyden and Kligman 1978).

1.2.1 antimicrobial treatment

Bacterial skin infections can be treated locally with antibiotics or antiseptics or systemically with antibiotics (burns present a special case and will be dealt with separately: see chapter 10.1). Which route of administration is best is still a matter of discussion (Leyden and Kligman 1978). Both routes of administration have their advantages and drawbacks. Important points to consider are the penetration of the antibiotic into the actual site of infection, hypersensitivity, bacterial resistance, and benefit/risk- and benefit/cost ratio's.

One of the advantages of local treatment is that high concentrations can be achieved at the site of infection without risking systemic side effects. This may be true in some cases, but not in all. First, a high concentration at the infection site may not be achieved because crusts, pus etc. often prevent the drug from reaching its site of action. Second, the absence of any risk of systemic side effects is subject of discussion. Systemic side effects due to locally applied antibiotics have frequently been reported, for example loss of hearing after local use of

aminoglycosides, but, as expected, tend to be milder than after systemic treatment. In systemic treatment active concentrations are generally achieved at the site of action, except in specific cases such as extensive deep burns (see chapter 10.1).

Two main problems associated with topical antibiotic treatment are bacterial resistance and hypersensitivity. These may also develop after systemic treatment, but this is less common. Hypersensitivity can develop quickly after topical use of antibiotics on the skin. This is dangerous as it can prohibit later systemic use in life threatening situations. Some of the antibiotics frequently used on the skin can be life-saving drugs. Cross sensitivity can prevent further use of a complete group of antibiotics (e.g. aminoglycosides). This has led to a general consensus that certain antibiotics, such as penicillins and sulphonamides should never be used on the skin (Leyden and Kligman 1978). There is still discussion about the aminoglycosides but it can be concluded that the use of these potentially life-saving drugs on the skin should be kept to a minimum. Leyden and Kligman argue that the prevalence of hypersensitivity to neomycin should not be exaggerated (Leyden and Kligman 1978). Neomycin was once used on a large scale in antiperspirants, but this did not cause as many hypersensitivity problems as could have been expected. But De Groot argues that reactions to cosmetics are generally underreported (De Groot 1988).

Resistance is quickly developed against antibiotics used on the skin. This is due to the presence of large numbers of bacteria and viruses on the skin, and particularly in skin infections, and fluctuating concentrations of antibiotic. This situation actually promotes bacterial resistance by selection. Large numbers of bacteria and viruses form an ideal situation for transduction of resistance. Transduction is the transport of bacterial DNA plasmid material from one bacterium to another by virus infection. Extensive use of antibiotics on the skin can lead to multiresistant bacteria and life threatening infections that cannot be treated. Cross resistance between similar antibiotics is generally a problem. Neomycin/gentamicin cross resistance is seen in *Staphylococcus aureus*, but only in less virulent organisms (Noble and Naidoo 1978).

Our conclusion on these points is that for antibacterial treatment on the skin one should never make use of drugs that are either:
a) reported to be sensitising, or
b) considered essential for systemic antibiotic treatment.
This also holds for any antibiotic within the same group or with the same mechanism of action. This excludes local treatment with aminoglycosides, such as neomycin, although these are included in the WHO essential drugs list.

Antibiotics are in general unstable chemicals. Preparations that contain water tend to have a limited shelf life. Tablets are generally more stable as they contain no water. Transport of tablets is easier and cheaper, this is important for Third World countries.

With respect to the therapeutical effects and side effects, the line between local and systemic treatment is not that sharp. Antibiotics will be absorbed after topical application, at least to a certain extent and systemic treatment may result in considerable concentrations on the skin (e.g.tetracyclines). Better penetration into deep infections is one of the main advantages of systemic treatment. Oral antibiotics were found to be more effective, especially in streptococcal infections. They were quicker in action with less therapeutic failures than antibiotics applied on the skin (Taplin et al. 1973; Leyden and Kligman 1978). Therapeutic failures should be avoided as in the Third World people often have to travel a long way to reach a doctor and should be spared a second voyage whenever possible.

Two choices can be made at this point: local/systemic and antibiotic/antiseptic. Local treatment is useful in uncomplicated superficial infections of the skin, but antibiotics should not be used in this cases. Simple antiseptic solutions will do (e.g. gentianviolet). Serious cases should be treated with systemic antibiotics, these may be administered by oral or intramuscular route. There is no place for topical antibiotics, except in the treatment of extended deep burns.

1.2.2 antibiotics

An antibiotic that is to be used in topical therapy must fulfil the following requirements:
- its spectrum of activity must include the relevant pathogenic species;
- it must be stable in nonocclusive dermatological preparations;
- the incidence of bacterial resistance must be low;
- it must be nonsensitizing; as sensitization may preclude its use for the same individual in life

threatening situations.
The following (groups of) antibiotics have gained acceptance as antimicrobial drugs:

* Tetracycline is active after both topical and oral use, and it is generally well tolerated. In the presence of water it is unstable, the shelf life of tetracyclines in aqueous solutions is limited to 24 hours at 20°C. The decomposition products of tetracyclines are toxic. Tetracycline is excreted through the skin after oral administration. A major problem in tropical countries is the risk of photosensitivity. Adequate protection against sunlight is essential if this complication develops. Local use of tetracycline is not feasible in the tropics but there may be a place for oral tetracyclines in severe acne.

* Chloramphenicol is active, moderately sensitising and reasonably stable, solutions have a shelf life of 4 months at 20°C. Its use should be limited to life threatening situations because of the risk of bone marrow depression. This side effect is seen in two forms, one dose related, reversible, the other apparently not dose related, irreversible. The latter usually results in a fatal aplastic anaemia. If chloramphenicol is used on the skin the risk of dose related bone marrow depression will be minimal, but the risk of non dose related severe aplastic anaemia can be as great as when it is used orally. Chloramphenicol is a life-saving drug in meningitis and should be reserved for this indication. It should not be used for trivial skin infections.

* Neomycin is active in skin infections but is has a relatively small spectrum of action. As it is relatively non toxic to streptococci it should be combined with other antibiotics, such as bacitracin. Neomycin is stable, aqueous solutions have a shelf life of one year at 20°C. Hypersensitivity is not uncommon, this is important as cross sensitivity to other aminoglycosides may be expected. Systemic side effects to local aminoglycosides may occur, such as loss of hearing.

* Gentamicin has the same general properties as neomycin. It could have a very limited place in local therapy for the treatment of heavily contaminated extensive deep burns that do not respond to silver nitrate or silversulphadiazine (see chapter 10.1).

* Bacitracin is generally combined with neomycin. The combination is active against streptococci. Bacitracin is generally well tolerated but unstable, in aqueous solutions it should not be kept in store for more than 48 hours. It can only be used in water free preparations, and even those should be kept cool. It has no place in tropical dermatology.

* Erythromycin and clindamycin are small spectrum antibiotics that are generally well tolerated and have a place in acne therapy in developed countries. Their usefulness in tropical regions is limited owing to their instability in the presence of water, and the high cost.

* Fusidic acid is another antibiotic that is unstable in the presence of water. It is less active in the presence of blood and pus. It can be used for resistant staphylococci, and has a place in western countries for treating difficult staphylococci. It can be used systemically but resistance will develop quickly. In Third World countries where the main problem is not staphylococci but streptococci there is no place for fusidic acid.

* Mupirocin is another antibiotic for use in resistant staphylococcal infections. It can only be used locally because it is very quickly eliminated from the body after systemic use (Van der Wal 1988). It has a very limited indication and can not be considered essential for tropical dermatology.

None of these antibiotics is considered suitable for use in local therapy in the Third World. The neomycin/bacitracin preparation of the WHO essential drugs list is not included in the formulary because we consider neomycin too sensitizing and bacitracin not stable enough. If local treatment is given some antiseptic should be used. In systemic infections and systemic treatment of skin infections there is a place for systemic antibiotics, they will not be dealt with in this report. The choice for a systemic antibiotic should form a part of a coherent antibiotic policy

aimed at minimizing the risk of development of resistance and optimising rational use of antibiotics available.

1.2.3 antiseptics

Antiseptics differ in some aspects from the antibiotics described above (see chapter 10.1). One of the important differences is that resistance is developed against practically all antibiotics, whereas in the case of antiseptics resistance is only developed against some drugs. Development of resistance can be an important criterium for making a choice for an antiseptic.

Some antiseptics are:

* Chlorhexidine is relatively cheap and well tolerated. It has a quick action, with residual activity. It is still active in the presence of blood and pus and it is non-toxic to human cells. There is one report on delayed wound healing in rats treated with chlorhexidine; clinical relevance of this effect is uncertain (Mobacken and Wengström 1974). Resistance does occur and is increasing in the developed world. Infections with resistant micro-organisms are a great problem, especially in hospitals. Chlorhexidine is reasonably stable but its decomposition products are toxic (see chapter 12.3). Decomposition products can cause hypersensitivity. Chlorhexidine digluconate is available as a solution only, the 20% concentrate is a better choice than the 5% solution included in the WHO essential drugs list, because the latter also contains a detergent and a colouring agent. These are not necessary, and may provoke side effects. In addition, transport of a 20% solution is more efficient and thus cheaper. For use in tropical countries chlorhexidine diacetate may be more appropriate as this is available as a powder. In the absence of water it is more stable, as hydrolysis will be minimal. Diacetate can be dissolved when needed. Concentrated stock solutions of diacetate cannot be prepared because the limit of solubility is close to the recommended in use concentration. The choice of either the digluconate or the diacetate will depend on the local situation and the health care system.

* Cetrimide is both an antiseptic and a detergent. It is generally combined with chlorhexidine as the combination has a better activity and the risk of resistance is diminished. It is generally well tolerated but allergic and necrotic skin reactions have been reported after repeated use. Cetrimide should therefore not be used for long-term treatment or as a routine antiseptic.

* Iodine has a good activity and a quick action, also against bacterial spores and virusses, but it is unstable and expensive. It stings and stains. Iodine can be absorbed, therefore frequent use or use on large parts of the body should be avoided, as the thyroid function may be influenced. Resistance to iodine is not likely to develop. Povidone iodine (betadine) has somewhat better characteristics but it is more expensive. Stability of povidone iodine is limited as the iodine is liberated at 43°C and higher.

* Chlorine and chlorine releasing preparations have been extensively used as antiseptics. They are still in use for technical disinfection in western countries. Their use as routine antiseptics is limited. Chlorinated lime and hypochlorite solutions may however be used as cheap and effective antiseptics. Resistance is not likely to develop. Hypochlorites are most active in slightly acidic solutions, but they are only stable in alkaline solutions. Solutions should thus be freshly prepared from powders or from concentrated alkaline stock solutions. Hypochlorites may cause dissolution of blood clots and bleeding. Hypochlorites are rapidly inactivated by organic matter. The solution has a high alkalinity.

* Potassium permanganate is cheap, has a quick action and resistance is not likely to develop. The solution is inactivated by all kinds of organic matter, this includes blood, pus, cotton swabs used for application of solution and the skin itself. Hence it is very short-acting. It can not be kept in the form of dilute solution as it is very unstable, but it can be easily prepared from stock solution. As it dissolves slowly and crystals or strong concentrations can cause severe chemical burns on the skin it is better to dispense a stock solution than the crystals themselves. Potassium permanganate is very useful for antiseptic bathing, combining mild antiseptic action with astringent action.

* Silver nitrate is expensive. It is active, non sensitising and well tolerated, but it has a very small therapeutic window; 0.1% is ineffective, 0.5% is effective and 1.0% is toxic. If used on large parts of the body, as may be the case in extensive burns it can cause hypochloraemia due to precipitation of silver chloride in tissue. Silver nitrate stains skin and clothes. Silver nitrate is useful for the primary care level treatment of burns and for the treatment of leg ulcers. Burns will be dealt with separately (see chapter 10.1).

* Gentianviolet and other triphenylmethane dyes can be used for pyodermas caused by streptococci and staphylococci, and for candida infections of skin, mouth (thrush) and vagina. The solution stains, if used on wounds stains may be permanent, hence it should not be used in the face. The 1% solution of gentianviolet was selected for the WHO essential drugs list. There are some problems with this preparation:
  - Literature suggests gentianviolet 1% could cause necrotic reactions, especially if used on intertriginous regions. Literature suggests more diluted solutions (0.5% or below) should be used (Meurer and Konz 1977).
  - Literature suggests gentianviolet is relatively ineffective in streptococcal infections (Speck et al. 1977; Churchman 1912). As skin infections in the Third World are more often due to streptococci than to staphylococci and streptococci are generally more dangerous (Taplin et al. 1973), gentianviolet may not be an optimal anti-infective for use in the tropics.
  - A rationale for using a combination of gentianviolet and brilliantgreen might be the observation (Moats and Maddox 1978) that gentianviolet was less effective at pH 6 and below whereas brilliantgreen was less effective at pH 7 and above. These effects were more pronounced with Gram negative organisms. As the pH of the human skin is between 5 and 8 the combination may be more effective than the separate drugs.

  In an in vitro investigation we found gentianviolet to be active against streptococci of groups A and B at concentrations far below 0.5%. These streptococci are the ones generally found in skin infections. The activity against *Candida albicans* and *Staphylococcus aureus* was even better. The activity against Gram negative organisms was more variable, *Pseudomonas aeruginosa* was the least sensitive to gentianviolet. We concluded that a 1% solution is too strong as this may cause side effects. We consider the 0.5% solution adequate. Investigations on the activity of gentianviolet and brilliantgreen and the relation to pH showed some effect of the pH value on the activity of both gentianviolet and brilliantgreen. This effect however was only slight. The minimal effective concentration remained far below 0.5% We therefore conclude that the 0.5% solution of gentianviolet is appropriate. A summary of the investigations is included as addendum A.
  Related triphenylmethane dyes are suspected carcinogens (Rosenkranz and Carr 1971), but carcinogenicity has not been proven. Gentianviolet is, for theoretical reasons, still suspected but carcinogenicity has not been shown.

* Sulphur has been used extensively in dermatology because of its keratolytic effect and because of a supposed antimicrobial effect. Its indications were once: acne, seborrhoic dermatitis, tinea versicolor, other superficial dermatomycoses, scabies, rosacea, perioral dermatitis, warts. Sulphur is still in use for acne, seborrhoic dermatitis, scabies and tinea versicolor (Lin et al. 1988).
  Sulphur is nontoxic and safe in normal use, even when used in small children (Anon. 1982; Lin et al. 1988).
  The keratolytic effect of sulphur is probably due to the reaction between sulphur and cysteine in keratinocytes, as a result of which cystine and hydrogensulphide are formed. Cystine is a normal constituent of the stratum corneum, this reaction thus seems to promote keratinization. On the other hand, hydrogen sulphide dissolves keratin. The effect on keratinization depends on the concentration used, in low concentrations sulphur promotes keratinization, resulting in para- or hyperkeratinization; in higher concentration keratinolysis due to hydrogensulphide predominates (Lin et al. 1988).
  The supposed antimicrobial effect depends on the conversion of sulphur to pentathionic acid. In plant disease models this mechanism has been studied. Hydrogensulphide may also play a role. In human skin, this mechanism has not been studied. It is thought that sulphur is converted to pentathionic acid by the normal skin flora or by keratinocytes. It has been shown

that sulphur is converted on the human skin to hydrogensulphide by keratinocytes. (Lin et al. 1988; Anon. 1982).
The hypothetically active substance (pentathionic acid) is known in inorganic chemistry. The free acid is unstable and breaks down rapidly into sulphur and sulphurdioxide. The pentathionate ion is somewhat more stable (Wiberg 1985; Cotton and Wilkinson 1972). In vitro investigations with this compound are therefore difficult to perform. So in vitro investigations should be aimed at forming this active compound in situ.
In our in vitro tests sulphur itself did not inhibit growth of the micro-organisms tested (*Staphylococcus aureus*, group A and B streptococci, *Candida albicans*), neither did it inhibit growth of a culture of normal human skin flora. These observations are consistent with literature (Anon. 1982). In none of these cultures the characteristic odour of hydrogensulphide was observed (Bakker 1989). On an agar medium, heavily inoculated with normal human skin flora and mixed with sulphur, growth of *Staphylococcus aureus* was not inhibited as compared to growth of this same organism on the same medium without sulphur added, but with the same human skin inoculum (Bakker 1989). This human skin flora did not seem to be able to produce from the sulphur any substance toxic to *Staphylococcus aureus*.
There did not seem to be a feasible in vitro model to test the antimicrobial effectiveness of sulphur. In literature no such in vitro model could be found. The best way therefore to investigate the antimicrobial effectiveness of sulphur seems to be by clinical investigation. Clinical investigations on sulphur alone have not been found in literature (Lin et al. 1988; Anon. 1982). Sulphur is still used in dermatology, with good results claimed, but usually in combination therapy. No conclusions about the antimicrobial effectiveness of sulphur can be drawn from these articles (e.g. Bamford 1983).
Keratinolytic agents usually have some effect in superficial infectious skin diseases, because they accelerate elimination of diseased parts of the horny layer. Some remarks can be made concerning these effects of sulphur:

- There is an effect on keratinization.
- Keratinolytic agents are effective in acne, seborrhoic dermatitis and dermatomycoses (e.g. salicylic acid).
- In scabies a positive effect of keratinolytics is to be expected.
- On human skin hydrogensulphide is formed, which is toxic to some organisms (e.g. *Sarcoptes scabii*). The formation of hydrogen sulphide seems to depend on the presence of keratinocytes and has not been observed in vitro.

The following conclusions can be drawn: a) An antimicrobial effect of sulphur can not be proven in an in vitro test. b) Sulphur should be tested clinically, comparing it with placebo and with keratinolytics such as salicylic acid. There are no publications available on such investigations; c) An anti-infective effect of sulphur can be expected but may be due to its keratinolytic action alone. In this case there is no need to place sulphur on an essential drugs list; salicylic acid will be the drug of choice.

1.2.4 conclusions

Trivial superficial skin infections can be treated with topical anti-infectives; in tropical Third World countries, antiseptics are the most appropriate. Antibiotic treatment should be avoided in trivial infections to prevent development of bacterial resistance. This applies to both local and systemic treatment. Serious or deep infections should be treated with systemic antibiotics, except for burns.

For use in primary health service gentianviolet solution is most appropriate. It should be used in the form of 0.5% gentianviolet. Gentianviolet should be available to the village health worker as a powder for solution. In powder form it is easily transportable. Chlorhexidine and iodine (or povidone iodine) can be used in hospitals and have a place as surgical antiseptics. Surgical antiseptics are, in contrast to antiseptics used for treatment of infection, not intended to remain on the skin for longer times, they must have a quick action. Both drugs meet this criterium. Iodine has a somewhat broader spectrum of action while there is no risk for resistance.
Potassium permanganate stock solution and silver nitrate solution also have a place in primary care level treatment.

1.3 treatment of burns

Burns can be divided into partial thickness burns and full thickness burns. In partial thickness burns the skin is only partially destroyed and possibilities for repair are still present. Skin functions are still present to some extent. Some blood vessels are still delivering blood, with nutrients, immune factors etc. As the nerves are functioning there is pain. In full thickness burns all skin functions are destroyed and no pain is felt. No spontaneous repair is possible and immune response is totally lacking. In very small full thickness burns this situation is less dangerous as some skin functions can be maintained from nondestroyed neighbouring parts of the skin. Repair from vital surrounding skin is possible in very small full thickness wounds.

Treatment of full thickness burns is different from treatment of other wounds and partial thickness burns. Surgical techniques are necessary for repair. As there is no immune response and systemic antibiotics will not reach the site of action, infection is extremely difficult to treat. Systemic complications and other problems lead to high mortality rates. Treatment of burns is best done in specialised burn care centra.

As treatment of infections is practically impossible, prevention is essential. The only way to achieve this is by local application of anti-infectives. The aim of treatment is to keep the burn wound sterile. Infection makes skin transplantation practically impossible as transplants are usually rejected in the presence of micro-organisms. This implicates that prophylaxis should be available at primary health care level and health workers should be able to start prophylaxis immediately.

There is a place for systemic antibiotics in treatment of burns for bacteriaemia and for treatment of infection in minor burns.

1.3.1 available preparations

* Mafenide acetate is used in the form of a 11.2% cream. It has a broad spectrum of action, and is active in the presence of blood and pus. Mafenide is absorbed and inhibits carbonic acid anhydrase. This causes acidosis and hyperventilation. It should not be used if any respiratory complications are present. Mafenide is a sulphonamide and causes relatively often hypersensitivity and pain when applied. On absorption it can cause the general sulfonamide side effects, such as nausea, headache and dizziness. Due to the high solubility of mafenide there is no risk for crystallurea. Mafenide inhibits rejection of necrotic tissue, this necessitates proper care of wounds. However this is not a side effect specific for mafenide as rejection of necrotic tissue is thought to result from microbial action. This effect is inherent to the anti-microbial activity of mafenide and is seen with all other anti-infectives (Moleski 1978). Mafenide is relatively stable. Resistance develops but may not be relevant in normal clinical practice.

* Silver nitrate solution is used with compresses. Creams were found to be less effective (Lowbury et al. 1976; Moleski 1978). It has a very small therapeutic window, but in a 0.5% solution it does not inhibit human cells and wound repair. Silver nitrate therapy should be started as soon as possible as it has a preventive, rather than a curative effect. Compresses should be kept wet at all times and good wound care is essential. Rejection of necrotic tissue is inhibited. Silver nitrate has a limited shelf life in solution, but solutions can be easily prepared if materials are available to ensure the right concentration. Silver nitrate solutions are selfsterilizing. If clean water is used for the preparation of silver nitrate solutions, they need not be sterilized. Advantages of silver nitrate are a broad spectrum, no relevant resistance problem, no sensitization, painless application. Disadvantages are the risk of electrolyte disturbances due to the reaction of silver with chloride, and staining. Staining can be a serious problem because it can make wound care more difficult because it complicates the distinction between necrotic and living tissue (Moleski 1978; Cason et al. 1966). In rare cases infection with nitrate-reducing micro-organisms has led to methemoglobinemia.

* Silversulphadiazine is used as a sterile cream. The silver ion is bound to the molecule and the drug is thus lacking some of the disadvantages of silver nitrate. There is no risk of electrolyte disturbances due to therapy, and methemoglobinemia will not occur. Staining will not be a problem. Silversulphadiazine is the preparation on the WHO essential drugs list for treatment of burns.

  Silversulphadiazine does not penetrate the wound so therapy is aimed at prevention rather

than treatment of infections. Silversulphadiazine inhibits, like the other drugs, rejection of necrotic tissue. Application is painless and the antimicrobial spectrum is broad. Compared to silver nitrate it is less effective against *Proteus* and *Pseudomonas*, but more effective against coliform Gram negatives. Resistance against silversulphadiazine is more likely to develop and has been reported more often in recent years (Lowbury et al. 1976). One major drawback of silversulphadiazine cream is its physical and chemical instability. It is best kept below 25°C. We demonstrated physical instability at 40°C. This means it is not suitable for primary care level in tropical countries. There may be a place for commercially available silver sulphadiazine cream in hospitals.

* Gentamicin has been used for the treatment of burns that were infected by a variety of micro-organisms. It was more effective in creams than in ointments. Some of the gentamicin penetrates through the wound, making treatment of an established infection possible. It has serious drawbacks. It is absorbed, and after absorption it impairs hearing and the renal function. Both are dose related side effects which occur occasionally if the cream is used on large areas of the skin. Gentamicin cream is expensive and because of large scale local use of aminoglycosides bacterial resistance is widely found, specially in *Pseudomonas* and *Proteus spp.* Sensitization reactions are not uncommon.

* Povidone iodine solution or ointment has been used in burn care. It has good activity but application is painful and systemic side effects, such as impairment of thyroid function, are to be expected. Iodine could inhibit proliferation of human cells and tissue repair. Resistance has never been observed. Most authors consider iodine or povidone iodine to be unsuitable for large wounds (>20% of the body surface) because of local and systemic side effects.

* Chlorhexidine compresses have been tried in the treatment of burns but they were painful and relatively ineffective, especially against *Pseudomonas aeruginosa* (Cason et al. 1966). In western countries chlorhexidine is sometimes used in combination treatment.

1.3.2 conclusions

In the treatment of burns, and especially in full thickness large burns, prevention rather than treatment of infection should be the aim. In order to keep the wound free from infection, treatment in full thickness extensive burns should be initiated as soon as possible. A preventive preparation should therefore be available at village level. The only preparation suitable for primary care is silver nitrate solution. This is best prepared freshly before use, but solutions may be kept for a maximum of 6 months if adequately protected against light. The other preparations are unsuitable for primary care level. Severely burned patients should be transported to a hospital if possible and treated adequately. At hospital level there may be a place for silversulphadiazine and/or gentamicin cream provided the preparation can be stored at temperatures below 25°C. Very small or partial thickness infected burns (pain present) can be treated systemically. Prevention of infection is not crucial in this kind of burns.

Local production of creams or ointments for the treatment of burns should only be carried out if sterility can be guaranteed. This will not be possible in small, poorly equipped production units. Silver nitrate solutions are sterile if clean water is used for preparation. Hence, these solutions can be prepared in small scale production units.

1.4 treatment of ulcers in leprosy

In the management of ulcers of any type it is important to establish and, if possible, to treat the causes of the ulceration in combination with measures to acquire and keep healthy granulation tissue in the base of the ulcers during a period in which care is taken not to disturb the natural healing process.

Leprosy is the classic example of a disease which is often complicated by permanent nerve damage. However, permanent nerve damage caused by any other disease will lead to similar problems which need a similar care.

The management of dry skin in leprosy secondary to nerve destruction will be described in section 4.4. This section deals with the prevention and treatment of ulceration. Further information on the anti-infective agents, mentioned in this section, can be found in sections 1.2 and 1.5

from this chapter.

Brand and Fritschi (1985) gave an excellent overview of four different causes of tissue damage in insensitive limbs: (1) direct damage by high stress or by burns; (2) ischemic necrosis from continuous pressure; (3) repetitive moderate stres; (4) mechanical stress on infected tissue. They emphasise the point that people without sensation continue to use a wounded and infected limb and subject it to stress in spite of the infection. As this is the main cause of the loss of fingers and destruction of feet in leprosy, it is extremely important to teach patients that the only way to avoid permanent deformity and disability is to rest the wounded part of the body until it heals.

Preventive measures are more important than treatment (Christian 1988, Brand and Fritschi 1985, Watson 1986) but once an ulcer has been formed, measures should be taken to acquire healthy granulation tissue in the base of the ulcer. Rest is essential, at least for the diseased part of the skin and especially if complicated by a secondary infection and oedema. Oedematous limbs should be rested in a position above the level of the heart (left shoulder) with a free unpinched outflow.

If fissures or deep cracks have formed, they may act as an entry spot for infections. The callous skin around the fissures should only be mechanically removed if a sterile instrument is available. The depths of the crack should be painted once daily with a 0.5% solution of gentianviolet in water (Christian, 1988). If an abcess exists it should be opened widely and a free outflow of pus should be maintained. Any necrotic tissue parts should be removed meticulously. Minor infections may respond to rest and twice daily soakings with diluted potassium permanganate solution during fifteen minutes, or in a bucket with water and soap (Watson 1986). The extremely foul smelling of some ulcers responds quickly to soakings with a sterile solution of 1% metronidazole in 0.6% saline, or by systemic use of metronidazole. The literature on the efficacy of topical use of metronidazole is conflicting (Reynolds 1989), therefore we did not include this preparation in the formulary. More serious infections need in addition to local treatment a systemic course of antibiotics, if possible based on culture results. A failing formation of granulation tissue may be enhanced by the daily application of povidon-iodine powder or possibly hydantoin powder (Bogaert et al. 1990) in the ulcer. Once healthy granulation tissue has been formed in the base of the ulcer, rest is no longer necessary, provided the natural healing process will not be disturbed.

In ulcers of the feet and lower legs complicated by lymphoedema pressure bandages are needed to reduce the oedema formation. In case of a plantar ulcer excellent results may be expected with the application of a below knee total-contact plaster cast (Brand and Fritschi 1985). Clean ulcers in other areas may be dressed with zinc paste or with a zinc-impregnated bandage once in one to seven days, depending on the amount of secretion. A failing epithelialisation over healthy granulation tissue may be enhanced by the use of a variety of expensive semipermeable or impermeable hydrocolloid occlusive dressings (Mumford and Mumford 1988). Preventive measures should be taught and practised throughout the healing process. In the case of plantar ulcers protective footwear should be made availabe before the ulcer is healed (Brand and Fritschi 1985).

1.5 mycotic skin infections

Skin mycoses can be either deep mycoses or superficial mycoses. Both are more common in tropical countries than in the temperate zone. Pityriasis versicolor for example develops if certain conditions are met, such as high humidity and temperature, and is hence in tropical countries far more common than in temperate zones (Hay 1985).

Simple dermatomycoses can be adequately treated with simple topical medicaments and need not be treated systemically. These simple topical preparations are cheap and safe, in contrast systemic treatment is expensive and systemic drugs may have serious side effects.

For use in tropical climates simple, stable preparations are the most appropriate. Newer antimycotics, such as miconazole, are relatively expensive, antibiotics such as nystatin are unstable. These drugs should not be used in primary care level treatment but could be reserved for the treatment of severe cases in hospitals.

1.5.1 available antimycotics

a. time honoured preparations:

* Whitfield's ointment used to contain salicylic acid 6% and benzoic acid 12%, and a lot of side effects, sensitization and/or irritation were seen when this preparation was used. Lower doses are used now (e.g. 6% benzoic acid and 3% salicylic acid in UK and 5/5% in the Netherlands). Side effects and sensitization are less common now. The action of salicylic acid is thought to result from its keratolytic effect. This effect is more pronounced in 5% concentration than in 3% concentration, this may be an argument for using 5% salicylic acid in Whitfield's ointment. Whitfield's ointment is active against dermatophytes but not against *Candida spp.* Publications on clinical trials proving miconazole or others to be more effective than Whitfield's ointment are available, but effectiveness was compared after two weeks treatment (Sivayathorn and Piamphongsant 1979). This comparison is not justified as Whitfield's ointment is somewhat slower in action. Whitfield's ointment was as effective as clotrimazole if compared after four weeks treatment (Clayton and Connor 1973).
The emulsifying ointment formulation of Whitfield's ointment is reported to be more effective than the petrolatum formulation (Polano 1984). This is to be expected, as a potentiation of antimycotics by sodium laurylsulphate, an emulsifier of emulsifying ointment, has been documented (Fiedler et al. 1981). Whitfield can be dispensed as a cream too, and some authors consider this preparation to be somewhat more active. This can be explained easily because liberation from the cream is better than from the ointment and the drying effect of the cream may be an advantage. On the other hand, Logan and coworkers could not detect any difference in activity between the ointment and cream formulation, but their patients preferred the cream (Logan et al. 1987). In our opinion the choice for either 6/3% or 5/5% depends on local preference, as does the choice for cream or emulsifying ointment. Benzoic acid/salicylic acid in petrolatum (vaseline, soft paraffine) is less preferable as it seems to be less effective, is occlusive and can not be washed away.

* Gentianviolet can be used for Candida infections of the skin, mouth and vagina. The activity of gentianviolet in candida infections is reported in literature (Tausch 1977) and was seen in our experiments too (for more information see chapter 10.1). Other dyes are used but gentianviolet is the most suitable. Castellani's solution should be considered obsolete. Fuchsine is a suspected carcinogen, boric acid is toxic and should not be used, phenol and resorcinol are not the most appropriate local antimycotics.

* Sodium thiosulphate can be used for pityriasis versicolor (Hay 1986). It can be dispensed as crystals packed in suitable doses. For example in Africa most Coca Cola bottles have a capacity of 300 ml. Sodium thiosulphate may than be packed in 30 grams packages for dissolution at home in one Coca Cola bottle full of water. Stability- and preparation problems are minimal if this system is used. Sodium thiosulphate is well tolerated and non toxic, and it is very cheap.

* Selenium sulphide can be used for pityriasis versicolor too but local side effects are not uncommon and it is toxic on ingestion. There is no need for a second drug for pityriasis versicolor, and the non toxic thiosulphate is preferred.

* Clioquinol is not considered to be a drug of choice, neither for systemic nor for topical use. It is less effective against yeasts and its activity against dermatophytes is limited. After topical use it is generally well tolerated but sensitization and severe irritation have sometimes been observed. Clioquinol is nowadays a controversial drug because it may cause severe neurological disorders. This however is not likely to result from local use.
It can not be considered essential as cheaper and more active preparations are available, such as Whitfield's ointment and gentianviolet solution.

* Tolnaftate is used as an antimycotic. It may be somewhat quicker in action than Whitfield's ointment, but is more expensive too. In the Netherlands it is only used in combinations. Such combinations are about as expensive as miconazole cream, but they are not effective against

Candida spp. and act slower than miconazole. There seems to be no place for such preparations.

* Undecylenic acid is only a weak antimycotic, and quite expensive. There is no place for undecylenic acid on an essential drugs list.

b. newer antimycotics

* The imidazoles (miconazole, ketoconazole, itraconazole) are a new generation of antimycotics. They have a broad spectrum, they are active against dermatophytes and *Candida spp.* and some bacteria and they are non toxic (Svejgaard 1973; Degreef et al. 1975; Faergeman 1986; Hay 1986; Jones 1986). As they are new they are still patented and expensive. Miconazole is patented until august 1989. Relatively little information is available on the preparation of miconazole dosage forms.
Compared with the older antimycotic preparations like Whitfield's ointment their action is quicker, but they are equally effective (Clayton and Connor 1973).
There are only minor differences among the imidazoles in local use (Hay 1986). Miconazole can be used as this is the best known and prices might go down as patents run out and more preparations become available. For systemic use there are more differences between the imidazoles. Only ketoconazole and itraconazole are effective in oral treatment, but the former has some serious side effects. Itraconazole is a very new imidazole that can be given by oral route. It is claimed that itraconazole has fewer systemic side effects, but too little clinical experience is available to prove this. These drugs are expensive.

c. antibiotics

* Nystatin is an effective antibiotic for candida infections, but it is extremely unstable. It is as effective as miconazole or other imidazoles (Hay 1986). It can be used in topical preparations, but systemic use is not possible as nystatin is too toxic. Amphotericin B can be used in systemic treatment. Both antibiotics are unstable. Nystatin can be kept for 6 months if stored in absence of water and below 5°C. These antimycotic agents are thus not suitable for use in primary care level, but can be valuable for specialistic hospital use.

* Griseofulvin can be used by oral route only. It is used in dermatophyte infections of hair and nails and in widespread dermatophyte infections of the skin. It is expensive.
Photosensitization has been described but is rare.

1.5.2 conclusion

In dermatophytosis we consider Whitfield's ointment or cream the drug of choice for the primary health care level. The risk of sensitization is considered very small.

In candidiasis gentianviolet solution is the drug of choice (solution of 0.5% in dermal candidiasis). This solution may be used in oral candidiasis too but one has to be careful that it is not swallowed. In pityriasis versicolor, sodium thiosulphate is the drug of choice. It should be dispensed in 30 grams packets with adequate directions how to prepare the solution.

Complicated or non responding cases of both candidiasis and dermatomycoses can be treated with topical miconazole. Systemic drugs may be used in certain cases, they form no part of this book but will be mentioned briefly below. Miconazole cream is stable and can be used in tropical climate.

There is little need for another antimycotic for topical use. Nystatin can be useful for well equipped hospitals, but the necessity for cooled storage will cause transporting problems.

Systemic drugs are essential for deep mycoses, systemic mycoses, and mycoses of hair and nails. Dermatophyte infections respond to griseofulvin and to ketoconazole or itraconazole. Griseofulvin is much cheaper and preferable if no photosensitization has occurred. If more information will become available on itraconazole, this may in future be the drug of choice for systemic treatment.

1.6 scabies and other parasitic skin diseases

Scabies and lice are cosmopolitan diseases but their incidence is generally higher in Third World countries than in the developed world, due to socioeconomic factors such as over-crowded houses. Both infections are contagious and are transmitted by close contact. Treatment of all contacts is necessary to prevent reinfestation. Frequent reinfestation can make treatment of scabies cases a frustrating affair. Prevention and education must be part of scabies treatment.

Other parasitic skin diseases occuring in the tropics:

- Larva migrans (creeping eruption) is a nematode infestation of the skin. The infestation is usually self limiting as the larvae die after some time, usually within six months. Secondary infections may complicate the disease. In most parts of the world, larva migrans is not a common disease and we do not consider drugs for larva migrans essential in our formulary. However, if the disease is frequently found in a region, tiabendazole topical suspension could be added to the list, but it is not included in this formulary.
- Jiggers and ticks should be removed as soon as possible. In most regions people know how to do this, drug treatment is not necessary.
- Guineaworm should also be removed by hand or any other simple method. In regions where guineaworms are generally seen people know how to deal with them. Prevention against guineaworm is essential.

1.6.1 scabicides

Benzylbenzoate is generally effective against scabies, but this has not been proven in controlled clinical trials. It is less effective than lindane. While lindane is effective after a single application, benzylbenzoate should be applied at least two times. Sensitization has been observed but is not common. Benzylbenzoate is generally non toxic. The lotion contains 25% of benzylbenzoate and is much more expensive than lindane lotion. The cost of treatment with benzylbenzoate is about ten times higher than with lindane.

Lindane has a deep action in the skin, and is thus more effective against scabies. Single application of a 1% lotion, cream or ointment is sufficient for a total cure of scabies (James 1971; Rasmussen 1981; Shacter 1981). Lindane is well tolerated. Sensitization to lindane is uncommon. If used correctly, toxicity is low. Bathing before the application of a lindane preparation is not necessary and enhances absorption. It should therefore be avoided (Rasmussen 1981; Shacter 1981). Lindane treatment should not be repeated. As itch may persist for weeks after all the mites have been killed, good information and in some cases an antipruritic are essential (Rasmussen 1981; Shacter 1981). Lindane is widely used in agricultural and household insecticides. This has led to an abundance of literature on the toxic effects of lindane. In contrast the toxicity of benzylbenzoate is not so well documented, but that doesn't prove benzylbenzoate to be safe (Rasmussen 1981; Shacter 1981). Lindane may be more toxic in malnourished people (de Bruin 1976).

Both lindane and benzylbenzoate can be used for the treatment of scabies and lice. Lindane can be diluted to a 0.1% preparation for use in lice treatment. In western countries, due to massive use of lindane, lice and occasionally scabies mites are found to be resistant to lindane. In tropical regions this will not be the case. In western countries malathion is used to treat lindane resistant lice. Its acute toxicity to human beings is greater than that of lindane. Malathion cannot be used for scabies as it does not penetrate the skin.

Resistant scabies is treated in western countries with pyrethrins. They too have a high acute human toxicity. Stability of pyrethrins is variable, depending on the type of pyrethrin used.

Sulphur is used for the treatment of scabies in small children and pregnant women. It is less effective than lindane and repeated application is necessary (Rasmussen 1981; Shacter 1981). Sulphur has various effects on keratinization, frequent local treatment may result in hyper- or parakeratinization (see chapter 10.4). Sulphur is no drug of first choice but it may be used in small children.

Other scabicides such as crotamiton or DDT are generally more expensive and less effective than lindane, and may have a higher toxicity. Crotamiton frequently causes irritation and sensitization is not uncommon.

1.6.2 conclusions

Lindane is the drug of choice in scabies and lice treatment. It should be used only once and the application should not be repeated. It can be used for small children as well as adults, but proper instruction on the use of the preparation is absolutely necessary. A cream preparation seems to be the most suitable, but lotions or ointments are also satisfactory. Benzylbenzoate can be reserved for those patients who are not responding to lindane or for patients for whom lindane is contraindicated. It should be kept in mind that the 'safety' of benzylbenzoate is less well documented than the 'toxicity' of lindane.

Lice can be treated with 0.1% lindane but in many cases drug treatment is not necessary, as frequent hair combing and washing of clothes can be effective measures.

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2 Corticosteroids

2.1 introduction

Corticosteroids have general anti-inflammatory, antipruritic and antimitotic properties. This makes them useful for a great number of skin diseases such as eczema, psoriasis and many others. Corticosteroids inhibit both inflammation and immune responses and can be used in immune disorders. They should not be used in infectious diseases. Infections are a contra indication for corticosteroids. Corticosteroids can be administered by mouth, injection or by local application. For primary care level treatment of skin diseases only local preparations should be used.

2.2 side effects

Topical corticosteroids have local and systemic side effects. Systemic side effects may occur after absorption of steroid. If corticosteroids are to be effective some penetration is necessary and some absorption inevitable. In children, because of their relatively large skin area, systemic side effects are more likely to occur. Once absorbed corticosteroids interfere with the cortico

steroid synthesis in the adrenal glands. Production is inhibited and depletion of corticosteroid reserves may occur. This results in decreased stress adaptation possibilities. If too much absorption takes place, especially of stronger steroids, the corticosteroid activity in the body may get too high. This results in effects on metabolism, Cushing syndrome and other systemic effects. In children growth retardation may result from corticosteroid use.

Local side effects include atrophia and striae. These effects result from an inhibition of collagen synthesis. Corticosteroids may change the clinical picture of skin diseases, thus making diagnosis difficult or even impossible. Masking of infections is an example of this. Hence the rule is to make sound diagnoses before starting treatment with corticosteroids. If corticosteroids are used in the face perioral dermatitis and acne may develop or aggravate.

All those side effects are inherent to corticosteroid use. Whether or not side effects occur depends on the strength of the steroid used, and the amount of steroid absorbed (dose and duration of treatment). Recent developments suggest that a separation of the effect on inflammation and the effect on collagen synthesis is possible. In future this may lead to the development of topical preparations with fewer local side effects (Dipetrillo et al. 1984; Schröpl 1985).

Sensitization to corticosteroids may occur but is very difficult to diagnose as the presentation of the reaction is changed by the steroid itself. Hence reactions will be underreported in literature. Sensitization reactions may result in an apparent aggravation of the skin condition treated or apparent treatment failures. Some steroids are probably more sensitizing than others (e.g. clobetasol) (Bachmann-Buffle 1983; Van Ketel and Swain 1981) but the relevance of sensitization in clinical practice is doubtful. Sensitization may be due to degradation products of corticosteroids rather than to the steroids themselves, but no sound evidence supports this hypothesis (see chapter 12.5).

2.3 weak and strong corticosteroids

Corticosteroids are generally classified according to activity:
class 1: weak: hydrocortisone acetate, dexamethasone;
class 2: moderate: triamcinolone acetonide, clobetason 17 butyrate;
class 3: strong: betamethasone 17 valerate, betamethasone dipropionate;
class 4: very strong: clobetasol 17 propionate.
This classification can only be of limited value as activity is not only determined by intrinsic activity but also by penetration. Penetration in turn depends on many factors such as formulation and the condition of the skin (Stoughton 1987; Poelman et al. 1984). Occlusion enhances penetration and thus activity.

2.4 selecting a corticosteroid

Selecting corticosteroids for tropical dermatology is difficult. The corticosteroids are comparable. Selection criteria can be the activity desired and the price. The strong corticosteroids are more difficult to handle because of their toxicity, and preparing homogeneous dosage forms can be difficult. Some corticosteroid esters are unstable (an example is betamethasone 17 valerate, see chapter 12.5). These are less suitable.

Weak corticosteroids are sometimes combined with penetration enhancers to obtain stronger preparations. Urea or salicylic acid can be used for this purpose. These creams have been reported to be very effective. For example, hydrocortisone/urea was as effective as betamethasone 17 valerate (Williamson 1987). These kind of clinical trials (Hillström 1984; Williamson 1987) have been done in only one indication, the specific trial mentioned above in dry eczema. The conclusions are therefore not generally valid as a considerable effect of urea itself has to be expected. Better results may be due to the enhanced penetration of hydrocortisone or to activity of urea itself in dry eczema. Hydrocortisone is less stable in the presence of urea or salicylic acid; this is a major disadvantage. It can be concluded that there is no place for fixed combinations of corticosteroids with urea or salicylic acid in tropical dermatology.

Hydrocortisone acetate is the weak steroid chosen for the WHO essential drugs list. It is widely used, generally available and inexpensive. It can be used in various preparations. Because of good stability creams and ointments seem most appropriate, shake lotions may be less suitable because they are less stable.

The strong steroid on the WHO essential drugs list is betamethasone valerate. We consider

this less appropriate, because it is less stable in most formulations. The stability is only acceptable in petrolatum and ambiphilic creams (see chapter 12.5). Dilution of commercially available strong steroid preparations is general practice throughout the world and may be cost effective (Smith et al. 1982; Stankler 1983; Kirsch et al 1983; Robertson and Maibach 1982; Magnus et al. 1981). The strong corticosteroid preparation chosen for the essential drugs list should thus be compatible with the diluents that are commonly used. Any strong or very strong corticosteroid without specific instability can be taken instead of betamethasone 17 valerate.

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3 Astringents

Astringents have been, and still are, extensively used, for example in antiperspirants and deodorants, but in some pharmaceutical preparations as well. The astringent properties of these drugs can be useful in soothing preparations, preparations intended for use in excessive perspiration, and in preparations intended for treatment of small wounds. Some of the astringents have antiseptic properties.

Most of the astringents that were once used on a large scale are considered obsolete. Lead- and bismuth salts should not be used because of their high toxicity after absorption. The soluble zinc salts are better avoided for the same reason. Tannins are either almost ineffective (hamamelis) or toxic; tannic acid may be absorbed and may affect the liver functions.

Potassium permanganate and silver nitrate are generally used as antiseptics. They have some useful astringent effects, but they should not be used as simple astringents because they are too toxic and irritating.

The most appropriate astringent for normal use is aluminium acetate. Aluminium acetate solutions are generally stabilised with tartrate, an acetotartrate is then formed. Aluminium acetate solution is also the astringent included in the WHO essential drugs list. It is used in solutions of various strengths and compositions. The use is traditional, effectiveness has not been proven. The vehicle (water) will play an important role and may be responsible for at least part of the effect. Controlled investigations comparing aluminium acetotartrate solution with the

vehicle, water, have not been reported.

Aluminium acetate solution is difficult to prepare and the preparation is expensive. Preparation temperature must be below 30°C, if temperatures rise above 30°C other, less active, aluminium salts are formed.

Aluminium acetate solution is not considered an essential drug by us due to its high cost, difficult preparation and doubtful therapeutic value.

4 Keratoplastic and keratolytic agents, moisturizers and antimitotics

4.1 introduction

Hyperkeratoses, dry, scaling skin, and cell-division disorders form part of many skin diseases (e.g. ichthyosis, psoriasis). The incidence of these diseases is more or less constant throughout the world (Porter 1977; Anderson and Maibach 1979).

Keratinization disorders may form part of the etiology of some skin diseases. One of the examples is acne vulgaris. The different categories of drugs for use in this kind of diseases are considered here as one group, because most of these drugs belong to more than one of the above mentioned categories. One example is urea that has a keratoplastic, moisturizing and weak antimitotic effect.

It is difficult to choose a drug in this category. One should carefully consider all the effects of the drugs as there may be many unwanted effects. For example if urea is used as a simple moisturizing agent the resulting skin thinning is an unwanted side effect.

4.2 keratoplastic and keratolytic agents

* Salicylic acid is a keratoplastic/keratolytic agent with practically no moisturizing or antimitotic effect in low doses. The drug can dissolve the kit substance in the horny layer, resulting in a keratoplastic effect (concentrations of 2 - 3%) or a keratolytic effect (above 3%). In higher concentrations (10% and more) it has a caustic effect. Due to its keratolytic effect salicylic acid enhances the penetration of corticosteroids (Hillström 1984). Salicylic acid has little antiseptic activity. Its usefulness in superficial infections is due to acceleration of shedding of horny layer. This effect is more pronounced at concentrations of 5% than at 3%, this may be an argument for the use of 5% salicylic acid in Whitfield's ointment. Acceleration of shedding of horny layer is useful in certain forms of acne. Salicylic acid may be absorbed, specially if used on large areas of skin or in children. Salicylic acid is useful if a keratolytic (or -plastic) effect is needed and a moisturizing effect is unwanted, such as in mycotic infections and in acne. It is useful in tropical countries and it is sufficiently stable; it may be kept for more than 2 years provided it is kept dry.

* Resorcinol has a keratolytic effect and some antimycotic and antipruritic effect. Absorption, even through healthy skin, is possible and systemic side effects, such as effects on thyroid gland and methemoglobinemia may be serious. On the skin resorcinol frequently causes irritation. As other drugs with fewer side effects are available, resorcinol should not be used.

* Benzoyl peroxide has a keratolytic, drying and bacteriostatic effect. It is widely used in Europe for acne. Irritation and sensitization are major disadvantages. The drug bleaches skin, hair and clothing. The raw material is explosive, it should be kept cool and moist. In Europe standardised quantities of water are added to benzoyl peroxide kept in stock. In tropical countries with dry climates this water may evaporate, resulting in dangerous situations. It is stronger than salicylic acid in acne, but due to its physico-chemical properties it is not appropriate for use in tropical countries.

* Retinoic acid and similar drugs accelerate both the formation and shedding of horny layer and may be useful in acne and some other skin diseases. They are used in both topical and systemic treatment. Its major use in Europe is in acne. The therapeutic effect in psoriasis is variable. Retinoic acid has serious side effects. It has little direct moisturizing effect (Grice et al. 1973). In concentrations normally used retinoic acid causes mild erythema and higher sensitivity of the skin to ultraviolet light. Pigmentation changes may occur. After application,

exposure to sunlight should be avoided. Retinoic acid and similar drugs are unstable compounds. Preparations should be kept in a refrigerator. They are not suitable for primary care level in tropical countries. The same holds for isotretinoin or etretinate tablets, they too cause hypersensitivity to sunlight and pigmentation changes. These drugs are very expensive.

* Tars are keratoplastic agents with weak antiseptic and antipruritic effects. They may be useful in psoriasis and eczema. The various products are usually prepared from wood or coal. They are cheap and effective in psoriasis and eczema, but cause a temporary discolouration of the skin that may be cosmetically unacceptable. Phototoxicity restricts the usefullness of coal tars but not of wood tars (Crow et al. 1961; Wiskeman 1971; Kaidby and Kligman 1977). Tars are difficult to handle during production and active constituents (phenols) may evaporate. Tars can be useful as an alternative for topical corticosteroids in psoriasis and eczema.

* Sulphur has keratoplastic and keratolytic effects but may have parakeratinization effects in lower concentrations. It is supposed, but not proven, that sulphur has some antiseptic effects. It has no moisturizing effect. It may be used in acne. In acne 2 to 5% is generally used. The antiseptic effect, if it exists at all, may enhance activity in acne. There may be a place for sulphur in primary care level therapy as it is cheap and stable, but it should be remembered that the activity of sulphur is still under discussion (see chapter 10.4).

4.3 moisturizers

* Urea has strong moisturizing properties but it has also keratolytic and antimitotic effects (Ashton et al. 1973; Boehm et al. 1974; Hellgren and Larsson 1974; Horsch and Wolf 1985). It is very useful for various dry hyperkeratotic skin diseases. Especially in ichthyosis its use is well documented (Swanbeck 1968; Pope et al. 1972; Anon. 1973; Blair 1976)
Urea may be used as a penetration enhancer for corticosteroids and other drugs (Williamson 1987; see chapter 10.2). Urea can be used in dry skin conditions, for example in ichthyosis, but epidermal thinning is a serious side effect to consider, especially in long term use. Urea is well tolerated. It is moderately stable, it may be used if certain precautions are taken (see chapter 12.8).

* Sodium chloride (household salt) has a moisturizing effect on human skin. It has no keratolytic or antimitotic effects (Hellgren and Larsson 1974). It is seldomly used in dermatology, but some dermatologists use it for the treatment of dry skin with satisfactory results (Boonk 1988). As it is readily available throughout the world and as it is cheap it would have been a good choice for primary care level if only more information was available. As any controlled trials, at least to our knowledge, are lacking the use of sodium chloride can not be recommended.

* Petrolatum and other occlusive measures like plastic wrappings have strong moisturizing effects with no antimitotic or keratolytic side effects. Petrolatum is relatively stable (see chapter 11.1); physical instability is not so important if petrolatum is used as the pure substance. There is no risk of epidermal thinning if petrolatum is used.

4.4 management of dry skin in leprosy

Leprosy patients often suffer from loss of normal sweat secretion secondary to nerve destruction. This will result in a dry skin. Dry skin is very liable to surface cracks in the dehydrated keratin layer. Infection, inflammation and ulceration may develop from such cracks especially on the palm of the hand and the sole of the foot. Also, dry skin looks bad and is slippery. It is therefore important that leprosy patients keep their skin hydrated (Brand and Fritschi 1985).

In these patients, normal sweat secretion does not occur. Therefore, water has to be supplied from the outside by soaking the affected skin in a water bath for 10 to 20 minutes. After the skin has been hydrated and excess water has been wiped off, petrolatum or some other oil has to be applied to keep this water in. The procedure should be repeated daily. This procedure has been taught generations of leprosy workers and can be found in a number of booklets on the subject (Brand 1986; Thangaray 1988; Watson 1986). A recent study quoted by Brand and Fritschi seems to indicate that the daily soaking procedure is not absolutely necessary, provided the petrolatum

or oil is applied regularly. Nevertheless, we suggest to stick to the old method that has been proven effective.

To keep the water in the skin, an inert, occlusive barrier at the lowest price is best. Therefore, we recommend the use of petrolatum. This is cheap and does not cause any adverse reactions (apart from the adverse effects of occlusion itself). However, local vegetable oils can be an excellent choice too, provided they do not have any sensitizing effects. Emulsifying ointment may be used too, but this is far more expensive than plane petrolatum. Expensive moisturizers, such as urea cream, do not seem to be any better for this indication than the soaking and occlusion procedure described above.

4.5 antimitotics

* Dithranol is widely used for psoriasis. The prevalence of psoriasis in Europe is about 2%, in East Africa this will be about the same while for West Africa a lower prevalence has been reported. Dithranol binds to DNA and inhibits mitosis. The exact mechanism is still unclear. White skin seems to be somewhat more sensitive to dithranol than black or coloured skin. Dithranol is highly active and should be used on diseased skin only. Care should be taken to avoid contact of dithranol with healthy skin. Dithranol has a limited solubility in paraffins of only 0.25%; it is practically insoluble in water. Preparations with more dithranol have a longer action (depot function). Dissolution is even more limited in preparations containing limited amounts of paraffins like lanette cream (35% paraffins, 0.1% dissolution) or zinc paste (50% paraffins, 0.13% dissolution). The problem with depot preparations is the risk of spreading the excess dithranol onto healthy parts of skin (Briedé 1982). Zinc paste is a relatively stiff preparation, spreading will be limited. Pastes are less occlusive than ointments and solubility of dithranol is less, this might be expected to limit activity, but limited activity has not been documented. Creams are even less occlusive and the solubility of dithranol is less, so they can be expected to be the least active preparations. Creams are indeed reported less effective in literature (Seville 1979; Wilson and Ive 1980; Whitefield 1981). On the other hand, dithranol cream may be rubbed into the skin and spreading of excess dithranol to healthy parts of skin will not be a problem (Wilson and Ive 1980; Briedé 1982).
  Dithranol may be dispensed in petrolatum or emulsifying ointment (occlusive and most effective), zinc paste after addition of 2% salicylic acid (less occlusive and less spreading) or lanette cream after addition of 0.5% ascorbic acid (less occlusive, no spreading but less effective also). Dithranol is unstable and should not be used in primary care level treatment. In those severe psoriasis cases in which dithranol treatment is really needed, this treatment should be given in a hospital.

* Podophyllium resin is an extremely toxic agent. It can be used as a caustic on serious warts and condylomata. If condilomata occur frequently in a region there can be a place for this drug but not in primary care level.

4.6 conclusions

In primary care level treatment there can be a place for salicylic acid (alcoholic solution) or sulphur (shake lotion) if a keratolytic and drying effect is wanted, as in acne, and for urea creams if a keratolytic and moisturizing effect is wanted (ichthyosis). Salicylic acid is included in the WHO essential drugs list, urea should be added.

Dithranol, podophyllium and tretinoin may be used in hospitals for various diseases if other drugs are ineffective, the first two are included in the WHO essential drugs list.

Coal tar is also included in the essential drugs list. There is a place for such preparations but phototoxicity restricts its usefullness in tropical countries.

Petrolatum or a local vegetable oil should be included for skin care in leprosy patients in regions where leprosy is a problem.

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5 Antipruritics

Itch can be a symptom of many skin diseases and of some systemic diseases as well (e.g. diabetes, scabies, uraemia, Hodgkin's disease). Before treating any serious itch, the underlying causes should be diagnosed and treated adequately. Treatment of the itch itself may be indicated in some cases. In scabies itch may continue for weeks after all the mites have been killed. Scratching may lead to secondary infections. If lindane treatment is repeated because people think they are still infected, this may lead to serious side effects.

In the treatment of itch the vehicle is very important. Cooling of the skin promotes itch relieve and placebo effects may be appreciable. Many drugs are available for treatment of pruritus but most are unsuitable. They will be mentioned briefly:

* Corticosteroids have direct and indirect antipruritic effects. Symptomatic relief of underlying diseases may play a role too. Corticosteroids cause some serious side effects like atrophia and should not be used if safer drugs are effective. Long term treatment should be avoided.

* Antihistamines are widely used on the skin for insect bites. The antihistamines are sensitizing drugs. Photosensitization is an important problem in climates with a lot of sunshine. These drugs should not be used on the skin.

* Local anesthetics may be effective in certain cases but not in all. Some are sensitizing (e.g. benzocaine). Lidocaine and pramocaine (pramoxine) are suitable for use on the skin, but they may not be effective in all cases.

* Menthol and camphor have some anesthising effect in low concentrations but have stimulating effects in concentrations of 0.25% to 1% generally used for antipruritic treatment. The stimulating effect on nerves in the skin changes the perception of itch. Menthol may cause contact dermatitis. Both menthol and camphor can be absorbed, even through healthy skin. In infants these agents may cause laryngospasms that may be fatal even after topical treatment; they should not be used in small children.

* Calmitol, a branded product, contains chloralhydrate, camphor, iodated oil, menthol, hyoscyamine, chloroform, ether and zinc oxide. This kind of preparation should not be used.

* Phenol has anesthetic, antipruritic and antiseptic properties. For use as an antipruritic 0.5% to 1% is used. As an antiseptic concentrations up to 2% may be used, concentrations above 2% may be caustic. Phenol causes various side effects. Local irritation and necrosis may occur, but sensitization is uncommon. Pigmentation disorders may occur. All reports on local side effects concerned concentrations of 1% or more. Phenol can be absorbed through the skin. Absorption through inhalation after use on the skin is possible. Local use of 0.5% seems to be reasonably safe. Precautions should be taken in the preparation of phenol containing drugs, as the pure compound is caustic and toxic. Phenol has a limited shelf life (see chapter 12.6).

In making a choice for an antipruritic both the vehicle and the active ingredient should be carefully considered. Shake lotions are most effective. The high pH of such preparations makes preservation often difficult. Calamine lotion is such a shake lotion. With 0.5% phenol it seems to be the best choice as the preparation is both active and stable at higher temperatures (see chapter 11.4). Side effects of phenol will be mild with the concentration used. Calamine lotion is also the antipruritic preparation of the WHO essential drugs list. Local anesthetics may be used too, but are more expensive and may not be effective in all cases.

6 "Indifferent" vehicles

In most dermatologicals the effect of the vehicle is substantial. This is not only placebo effect, but is also because of general effects of the vehicle ingredients on the skin. Vehicles may be soothing, occlusive, cooling or protecting. Vehicles therefore will never be "indifferent".

Although these vehicles contain no drug ingredient they may cause various side effects. Sensitization and irritation are frequently seen, for instance with preservatives and wool alcohols.

Some vehicles are useful in primary care level dermatology:

* Calamine lotion (see chapter 10.5). It contains phenol as a preservative and antipruritic. It has general soothing, drying and antiseptic properties. The lotion should not be used on large wounds as zinc may be dissolved and absorbed. Zinc may promote healing but it can also be toxic if large doses are absorbed (Hallmans 1978; Brüske and Salfeld 1987). Calamine lotion is stable under tropical conditions. The formula may be changed (see chapter 11.4) to obtain equally effective but cheaper preparations.

* Zinc paste is a protecting vehicle. It permits some water to pass through so it is not as occlusive as petrolatum. Absorption of zinc if used on wounds will be minimal as the zinc oxide particles will not come into contact with fluids. Zinc paste is an effective physical sunscreen

(see chapter 10.7). For tropical use the formulation of zinc paste should be adapted (see chapter 11.2).

* Petrolatum may be used as an occlusive agent or for its protective properties. It may be used as an hydrating agent (see chapter 10.4).

* Clean water may be used in various skin diseases. Due to evaporation on the skin it has a cooling and drying effect. It can be used in the form of hot or cold compresses.

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7 Sunscreens

Exposure to sunlight may cause acute and chronic skin damage. Adaptation mechanisms of the skin include epidermal thickening and pigmentation. Pigmented skin is less sensitive to sunburn.

In tropical countries sun protection is necessary for some people, for example people with a sensitive skin and white people. In some diseases (photosensitivity, systemic lupus erythematosus) and for albino people absolute protection is needed and normal sunscreens are insufficient. It would be wise if those patients would stay indoors for the time that protection is absolutely needed. Clothing may provide adequate protection if tightly knitted and dry. Loosely knitted or wet clothing may permit some radiation to penetrate (Anon. 1984).

Sunscreen agents can be divided into physical and chemical sunscreens. The physical sunscreens contain high amounts of powders that scatter sunrays, thus preventing any radiation from reaching the skin. They usually are cosmetically unacceptable. Zinc paste is an example of this class of sunscreens.

Chemical sunscreen agents absorb part of the radiation, thus providing some protection. Most chemical sunscreens, including PABA, have their peak absorption in the mid range ultraviolet spectrum (UVB; 290 - 320 nm). UVB is the major cause of sunburn. Tanning results from UVA (320 - 400 nm) and is not affected by these agents. Photosensitivity reactions too are often caused by UVA and these sunscreens cannot prevent them (Lane-Brown 1977; Anon. 1984). Some sunscreens do provide protection against UVA but protection is far from complete (Anon 1984). Photosensitivity reactions and reactions in lupus erythematosus cannot be prevented by chemical sunscreens.

Chemical sunscreens are characterised by two parameters, the sun protection factor and the substantivity. The sun protection factor is an indication of how much longer the skin may be exposed to sunlight. The substantivity is an indication of the tendency of the sunscreen to remain on the skin after sweating, bathing and swimming. The sun protection factor is difficult to define and tends to be dependent on various factors such as the vehicle used and the type of skin.

Most of the chemical sunscreens may cause (photo)sensitivity reactions themselves. Many may cause irritation. PABA causes staining of clothing.

There can be a place for a simple sunscreen in primary care level dermatology. PABA is a good choice as it has a high substantivity because it penetrates the skin. PABA is relatively cheap. PABA cream can easily be prepared. If strong protection is needed PABA is not effective enough but neither are the other chemical sunscreens.

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1 Dermatological preparations for tropical use

1 Ointments

1.1 introduction

Ointments are semisolid fatty preparations, in which solids or liquids may be dispersed. Types of ointments generally used in dermatology are hydrophobic ointments, that can absorb only small amounts of water, emulsifying ointments, that can absorb large amounts of water under formation of an oil in water cream, and hydrophilic ointments, that are completely water miscible. Fatty creams of the water in oil type are sometimes included in the ointment group too. The therapeutical properties of an ointment depend on the various oils and fats used in their preparation:

- paraffins make non washable ointments that do not penetrate the skin. Drugs used in these ointments have only superficial activity. Paraffins are occlusive.
- paraffins and water in oil emulsifiers are combined in ointments that are slightly more penetrating and less occlusive. Small quantities of water may be absorbed by these ointments, but they are difficult to wash away.
- paraffins and oil in water emulsifiers are the constituents of emulsifying ointment type vehicles. These are washable and may be used on hairy skin. They are not very occlusive and they often favour penetration of active ingredients incorporated in them. If water is added vanishing creams of the oil in water type result.
- the use of oils and waxes instead of paraffins results in more penetrating preparations.

1.2 gels

Fatty ointment bases are gels containing a solid and a liquid phase. They are liquid/solid heterogeneous systems. In sols and suspensions the solid phase particles may migrate through the liquid phase but in gels they are fixed in a three dimensional structure they have formed.

In order to form a stable three dimensional structure, the solid phase particles should be able to form secondary bindings with each other (van der Waalsbinding, H-bridges).

The stability of a gel depends mainly on:

- the form of the particles of the solid phase;
- the physico-chemical properties of the solid phase and their ability to form secondary bindings;
- the concentration of solid phase; and
- the physicochemical properties of the liquid phase.

Gels often are thermoreversible, this means they change into sols upon heating and back into gels again on cooling. Gel/sol transformations may occur under other circumstances too, for example if the gel is stirred vigorously. Formation of the gel system may take time, some gels harden during weeks after preparation due to further formation of the gel network. As the gel network tightens upon aging, some of the liquid phase may be pressed out; this is called bleeding or syneresis.

1.3 petrolatum

The properties of petrolatum (soft paraffine, vaseline) change with origin and supplier. Petrolatum contains solid alkanes forming a gel network in the liquid alkanes. The structure of the gel is characterised by so called "fransenmicellen". In this system branched solid i-alkanes have the best gel forming activity and unbranched solid n-alkanes are responsible for a higher consistency. The i/n ratio of the solid phase and the solid/liquid ratio of the petrolatum determine the characteristics of the resulting gel (Hüttenrauch 1970; Hüttenrauch et al 1977a;

Schmiedel 1984).

Upon heating the solid alkanes will melt and a homogeneous melt will form at higher temperatures. At intermediate temperatures (35 to 45°C) some of the solid alkanes are molten while others are still in the solid phase. This results in a smaller amount of solid gel forming phase and a larger amount of liquid phase. This will result in partial melting of the gel. This looks like bleeding, but is not the same. This phenomenon causes separation and petrolatum preparations thus should be mixed before dispensing or use.

1.3.1 ceresin

A way to stabilise petrolatum gels could be changing the solid phase, so that it consists of higher melting alkanes. This can be done by adding microcristalline wax or ceresin; the latter being the most appropriate because it has a favourable i/n ratio (Schmiedel 1984). In our experiments, the addition of ceresin however did not result in an ointment base that was stable at temperatures up to 45°C (Bakker 1988). This was not unexpected. The influence of solid/liquid- and i/n ratios tends to have only a slight effect on the melting characteristics of the ointment and on bleeding. A little less oil will be pressed out but this will not solve the problem at hand (Hüttenrauch et al. 1973).

1.4 cetostearyl alcohol

Another way to stabilise petrolatum gels could be the addition of another gel forming system. This has been done in emulsifying ointment (British Pharmacopoeia) and various other ointments. Various emulsifiers are used for this purpose such as cetostearyl alcohol, spans and glyceryl monostearate (Erös and Ugri-Hunyadvári 1977a; Führer 1971). These emulsifiers form a second, independent gel system.

1.4.1 polymorphism of cetostearyl alcohol

Cetostearyl alcohol can exist in various (liquid) crystalline states. This is called polymorphism. Pure cetostearyl alcohol will change upon heating at 38°C from the ß-modification into the α-modification, the latter melts at 51°C. In the α-modification the hydrophobic parts are more orderly arranged (parallel) than in the ß-modification (Boekenoogen 1964; Gunstone 1967; Chapman 1969; Nürnberg 1985). On cooling this molten cetostearyl alcohol it will solidify into the α-modification at 48°C and will slowly change over to the ß-modification below 23°C (Nürnberg 1985).

Cetostearyl alcohol may form a gel system in paraffins in both the α- and the ß-modification. The ß-modification however may be expected to be a better gelforming system than the parallel arranged α-modification. This effect will parallel the effect of temperature on the petrolatum gel itself (see chapter 11.1.2). If the ointment is prepared by melting it should be stored below 25°C for some time to allow a stable gel to be formed. This explains the maximum storage temperature of 25°C indicated by the British Pharmacopoeia.

1.4.2 other gelforming emulsifiers

The polymorphic properties of cetostearyl alcohol are caused by the presence of a fatty alcohol chain in the molecule. The same polymorphism may be expected from the other emulsifiers used in ointments. Pure fatty alcohols with an even number of C atoms prefer the ß-modification, those with an uneven number prefer the α-modification. Mixtures tend to prefer the α-modification (Boekenoogen 1964; Gunstone 1967; Chapman 1969). In stabilization of petrolatum gels the use of pure fatty alcohols with an even number of C atoms would give the best results. Normal pharmaceutical qualities of stearyl alcohol however contain enough by-products to allow the α-modification to exist at low temperatures (Boer and Cox 1978; Junginger et al. 1979; Führer 1987).

If other stabilisers are used the temperatures at which polymorphic changes occur may be different but they are in the same range. Hence this will not solve the problem. All systems we tested were partially melted and inhomogeneous at 45°C (Bakker 1988).

1.4.3 water and cetostearyl alcohol

If water is added to gel systems containing cetostearyl alcohol the picture is further complicated. In such a system one more phase will exist, the hydrophilic liquid phase. There will be a

water/fat interface. Cetostearyl alcohol has hydrophilic and hydrophobic groups and will prefer the interface layer. The hydrophilic group is small and the hydrophobic group is large. It may be expected that the α-modification with its parallel arranged hydrophobic groups will be more suitable to occupy the interface, and hence will be more stable (Erös and Ugri-Hunyadvári 1977b). The same holds for binary systems of cetostearyl alcohol and water. The stabilization of the α-modification in the presence of water has been reported in literature. If 20% water was added to cetostearyl alcohol the ß-modification changed upon heating into the α-modification at 14°C and melted at 56°C (Junginger et al. 1979; Nürnberg 1985).

The α -modification will form a more stable interface than the ß-modification because the α-modification with its parallel arranged hydrophilic groups fits better on the interface. This implicates that for use in creams coemulsifiers in the α-modification tend to give better results. This has also been reported in literature (Boer and Cox 1978).

In water containing ointments the gel structure will be more stable and will exist over a wider temperature range than in ointments that contain no water. Nevertheless, there may be more separation of oil because the α-modification is a less effective gel-forming agent. This was observed in practice (Bakker 1988). In creams with an oil in water structure the same effect will be observed but in this case separation of oil is impossible because every oil particle is surrounded by water.

1.5 plastibase

Plastibase is an ointment base containing 5% polyethylene 21.000 as a gelling agent in liquid paraffin. The quality of the polyethylene used is important. The gel is formed only under very specific cooling conditions. The mixture should be melted at 130°C and quickly cooled by pouring it over cold steel plates kept at a temperature below 50°C. If these conditions are not met a useless mixture of crystalline polyethylene and paraffin may result (Mutimer et al. 1956; Hüttenrauch et al 1972b).

Plastibase has an approximately constant consistency between -15 and 60°C. Molten plastibase will not form a gel again on cooling unless the specific cooling conditions described are met. In practice this means that if the gel melts, it will not be formed again on cooling. As in tropical countries temperatures of 60°C and above are no exception, for example during transport, plastibase is not an optimal ointment base for use in the tropics. Plastibase is not commercially obtainable as such.

1.6 inorganic gelling agents

It is possible to obtain stable gels by using inorganic gelling agents in petrolatum or other oils (e.g. Maes 1976). Aerosil gels in petrolatum showed excellent thermostability (70°C) (Bakker 1988). These gels are not widely accepted for use in dermatology because they cause a very unpleasant feeling on the skin.

1.7 other fatty ointment bases

Various other ointment bases are used in dermatology. Lanoline/petrolatum bases were, and are, widely used. Lanoline bases were less stable than petrolatum (Erös and Ugri-Hunyadvári 1977a). Lanolin (or wool fat) derivatives may cause allergic contact dermatitis, they should not be used (Schlossmann and McCarthy 1979). The reaction is probably due to alcohols in lanoline, so taking only the alcohol fraction like in wool alcohols ointment will not solve the problem (Schlossmann and McCarthy 1979).

Beeswax or other gelling agents were not appropriate as they did not form more stable gels (Bakker 1988).

1.8 microbiological problems with fatty ointments?

Any dermatological preparation is liable to contamination during use. Micro-organisms need water to grow. as well as some other nutrients. If bacteria cannot grow, they will die. As water is not available, fatty ointments will not promote bacterial growth.

However, Myers could detect surviving bacteria, even non-sporeforming species, in both vegetable and mineral oils for years after contamination. They did not grow but remained viable for long times (Myers 1969). Infection from an ointment contaminated during use or preparation may thus be possible.

1.9 conclusions

Ointments generally get inhomogeneous at temperatures that are easily reached in tropical countries. There are no appropriate preparations that have no risk of getting inhomogeneous during storage in tropical climates. Therefore, if ointments are to be used in tropical countries some precautions are essential. Before dispensing or using an ointment it should be stirred or mixed, because it may be inhomogeneous.

Plastibase is no alternative. Its properties are better than those of petrolatum, but they are n optimal. It is difficult to obtain and expensive. Local production of plastibase is not feasible.

Emulsifying ointment is most appropriate as a general ointment base for tropical dermatol- ogy, because it is washable (and hence may be used on hairy parts of the skin) and relatively non-occlusive. Petrolatum may be an alternative, but this is not washable and occlusive. Petrol tum with 10% wool fat may be used, but has the same disadvantages. In addition, wool fat has sensitizing properties. Water in oil creams are less stable and liable to microbial contamination and are not considered appropriate.

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2 Pastes

2.1 introduction

Pastes contain large amounts of solid phase in a hydrophobic (fatty) or hydrophilic liquid or semisolid base. They are soft, semisolid preparations. Calamine lotion is thus not considered a paste although it contains about 23% of solid matter.

Pastes are disperse systems. The properties of pastes depend on the type and the concentration of solid phase and the type of liquid or semisolid phase. Pastes containing water as a liquid phase are microbiologically vulnerable and may separate. Liquid preparations such as calamine lotion are preferred, because they are preserved and because they are easily rehomogenised.

The pastes considered here are hydrophobic pastes. Due to the high powder contents they are not occlusive, some may even absorb fluids and may have drying properties. Pastes may be used as protecting agents (e.g. against sunburn, see chapter 10.7), to fix drugs to certain parts of the body (e.g. in dithranol paste, see chapter 10.4) or as soothing agents. Most pastes do not melt on the skin and they do not promote penetration of active ingredients. They are only useful as vehicles for those drugs that have their site of action at the surface of the skin.

Pastes are difficult to wash off and are not intended for use on hairy skin. The best way to remove pastes is rinsing with some vegetable oil.

Various powder ingredients have been used for pastes. Zinc oxide and starch are amongst the most widely used. Starch has major disadvantages for tropical use as it is microbiologically unstable (Bos et al. 1989). The absorption of zinc after dissolution in wound exudates has been described (Hallmans 1978) but is unlikely to occur after use of pastes. In an in vitro investigation no zinc was dissolved in an acid medium from pastes (Von Czetsch-Lindenwald and Schmidt-LaBaume 1939). From hydrophilic preparations some absorption may occur, but whether this effect is relevant in a clinical situation is unsure (Brüske and Salfeld 1987).

Some lipids that are often used are petrolatum and vegetable oils. Petrolatum pastes have a less soothing effect and are less penetrating; they are used for fixation of drugs on the skin (e.g. dithranol) and as a protective. Pastes prepared with vegetable oil are more penetrating and soothing.

2.2 zinc paste

Many pharmacopoeias contain zinc paste or similar preparations. These usually contain 25% zinc oxide, 25% starch and 50% paraffins. These pastes have protecting properties but are not occlusive owing to the high powder content. The pastes are rather stiff. They may be used to fix drugs on the skin. These pastes showed physical stability at 45° and 70°C (Bakker 1988). Emulsifiers are sometimes added to a paste. This makes the paste washable so that it may be used on hairy skin. Unfortunately, pastes with an emulsifier showed physical instability at 40° and 45°C (Bakker 1988) and hence are less suitable for use in the tropics. Pastes that contain an emulsifier have other therapeutical properties than pastes without emulsifiers. Pastes with an emulsifier have a more penetrating effect because of the presence of the emulsifier and because the paste melts on the skin.

Zinc pastes usually contain 50% of powder phase. Pastes with less powder have other characteristics and hence other indications, and they showed physical instability at temperatures of 45°C or higher. Pastes with a lower powder content are thus not appropriate.

Pastes usually contain starch. Starch is thought to enhance the absorptive power of the paste because it is an absorbent itself. This seems to be untrue. Starch particles do not come into contact with the fluid that passes through (Von Czetsch-Lindenwald and Schmidt-LaBaume 1939). This was confirmed by our own observations that a zinc paste with 25% starch did not show any colouring if treated with iodine solution (Bakker 1988). Starch is widely available throughout the world but it has some serious disadvantages for pharmaceutical use. Starch is generally contaminated with various micro-organisms. During storage at higher relative humidity the raw material absorbs water and may become wet enough to allow microbial growth (Bos et al. 1989). This may result in contaminated pastes. Thus, starch is better avoided. As it is the

high powder content rather than the absorptive power of the ingredients used, 50% zinc oxide will result in a paste with the same general characteristics.

Western pharmacopoeias sometimes prescribe the addition of some liquid paraffine. This is done to improve the spreadability but it is not necessary. It can be left out.

Conclusion: pastes are suitable for use in tropical climates. A good and simple formula is zinc oxide 50% and petrolatum 50%.

2.3 zinc oil

Zinc oil contains zinc oxide (usually 60%) and vegetable oil. This is a (semi)liquid preparation with soothing and drying properties. Most oils may be used, but some can better be avoided as they may cause hypersensitivity reactions. This is for example the case with sesame oil. The acid value of an oil is a parameter that indicates the amount of free fatty acids in an oil. The acid value of an oil used for the preparation of zinc oil should not be too high as zinc oxide reacts with these acids. This results in a stiffer preparation with less long term stability. Oils with an acid value of 12 or less are suitable (Bakker 1988). Current vegetable oils have lower acid values, the oil need not be specified.

Zinc oil should not be packed in plastic containers as "corrosion" of the plastic material may occur. It should be stirred or mixed before dispensing or use, the package must allow this.

2.4 preparation techniques

Zinc oxide should be passed through a sieve before it is mixed with petrolatum or oil. This is necessary to obtain a homogeneous paste. However, if care is taken to mix small quantities of zinc oxide with small quantities of petrolatum at a time reasonably homogeneous pastes are obtained, and sieves are not strictly necessary (Bakker 1988).

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3 Creams

3.1 introduction

Creams contain at least one hydrophilic constituent, generally water, one lipophilic constituent and an emulsifier. Classical creams are disperse systems in which either the lipid is dispersed in the water phase (oil in water, o/w) or the water in the lipid phase (water in oil, w/o). The inner phase consists of small droplets that have some mobility. Ambiphilic creams in contrast consist of two continuous phases. In these creams it is no longer possible to distinguish an outer and an inner phase (Albert 1985).

Water in oil creams are not appropriate for use under tropical conditions as they are physically unstable (see chapter 11.1). Ambiphilic creams are newer and more complicated creams. They are quite fatty creams but relatively nonocclusive. They may be more appropriate than oil in water creams as unstable drugs are believed to be more stable in ambiphilic creams (Ray-Johnson 1981; Albert 1985), but this has not been proven. If enough information was available on these ambiphilic creams they might have been considered for tropical use, but this is not the case. Hence oil in water creams are the only types dealt with in this chapter.

Vanishing creams have a slight cooling effect on the skin due to evaporation of water after application. After evaporation of water a thin oily layer will remain on the skin. This has little occlusive effect and may even have a drying effect. Many drugs may be dispensed in creams but

incompatibilities are not uncommon and should be taken into account.

3.2 the cream system

The instability of a cream is caused by two mechanisms. The difference in specific gravity between the oil and water phases causes the lighter phase to float on the heavier one. This causes a separation process called creaming.

In a vanishing cream the oil phase is dispersed in the water phase. The oil forms small droplets. The smaller the droplets, the larger their relative area and their interface will be. This situation is energetically unfavourable. The system will strive for the most favourable situation, thus the smallest interface, thus the largest droplets, thus complete separation. Hence all emulsions will be unstable and tend to separate.

Creams must therefore be stabilised. There are two ways to do this, preventing contact of droplets (thickening agents) and preventing coalescence of droplets (emulsifiers). Emulsifiers are most widely used. An emulsifier has a hydrophilic part and a lipophilic part. The first wants to dissolve in water, the second in oil. Thus the emulsifier will accumulate at the interface. This is energetically a very favourable situation. The hydrophilic part of the emulsifier will resist being pulled into the oil phase, the other part will resist being pulled into the water phase.

Apart from the water and the oil phase other phases may exist in creams, such as various gel phases. This implicates that most creams are very complicated systems. The properties of a cream depend on the type and proportion of water and oil phases and emulsifier, and preparation techniques. These will be dealt with in the following sections.

3.3 the oil phase

Various fats and oils are used in creams, for example petrolatum, vegetable or synthetic oils and waxes. The latter (e.g. cetiol) are widely used in creams because the resulting cream is less greasy and more penetrating, and hence cosmetically more acceptable. Cetiol V (oleyloleate) is the most extensively used wax. Waxes have some major disadvantages, such as being more expensive, more difficult to obtain, less stable and being better solvents. Greater solvent power implicates that these waxes may inactivate preservatives. Drug penetration may be enhanced due to better penetration of the oil phase, or diminished due to greater affinity of the drug for the vehicle (Lippold 1984; Loth 1986). The overall effect depends on the properties of the drug too, this can not be predicted in general terms.

Vegetable oils have one important advantage: they will be available from local production in many countries. But they have many disadvantages too. They are less constant as far as quality and composition are concerned. They may be unstable (turning rancid upon storage). Oils are, like waxes, good solvents for many drugs and preservatives. Preservative inactivation by oils is especially important at tropical storage temperatures.

Paraffins are chemically indifferent and stable. They are far less efficient solvents for most drugs and preservatives. Paraffins are relatively cheap. Paraffine creams have less penetrating power and are more greasy on the skin.

Side effects resulting from oily phase components of o/w creams are rare. Some components (e.g. sesame oil) can better be avoided as they may cause sensitization. In rare cases, yellow petrolatum may cause sensitization reactions. Poor quality white petrolatum may cause irritation reactions because it contains traces of the bleaching agent. Because of general availability, low price, stability and indifference towards most drugs and preservatives we think paraffins are most appropriate.

3.4 the water phase

The hydrophilic phase consists mainly of water. As this is microbiologically vulnerable it has to be preserved (see chapter 11.3.6). Humectants such as glycerol or sorbitol may be added to prevent evaporation. Evaporation may occur in stored creams (stability problem) and after application (therapeutical problem). The surface area and surface properties are major determining factors, as are environmental factors such as humidity and temperature. Environmental factors are inevitable but cream properties can be manipulated. Evaporation from a capillary system is diminished with smaller capillaries. Creams form a cappilary system, in which the width of the capillaries depends on the droplet size. The droplet size will thus influence evaporation.

After application on the skin, water will evaporate and an oily layer will result. This may have some occlusive, and thus moisturizing effect, but it may have a drying effect too, depending on type of oil or fat and proportion used. If paraffins are used in appreciable proportions, as in our basic cream, the resulting cream will have a mild moisturizing effect and humectants cannot be considered necessary for therapeutical reasons.

Evaporation of water from stored creams will result in an oily top layer on the cream, preventing further evaporation. Unfortunately this happens only after half of the water has evaporated and hence it can not be considered a protecting mechanism. We determined evaporation losses from stored basic creams with humectants, and found no significant differences in evaporation rates between creams without humectant, with 4% sorbitol and with 10% propylene glycol. Evaporation losses were determined in jars (diameter 49 mm) without closure, containing 10.0 grams of cream, stored at 45°C (Bakker 1988). Although evaporation is a poorly reproducible process, it may be concluded that humectants will not prevent a stored cream from drying out. As they are expensive they should not be used.

3.5 emulsifier

Emulsifiers are characterized by the hydrophile/lipophile balance (HLB). The HLB value is defined as the hydrophile percentage of the molecule divided by 5. Dependent on the type of emulsion desired, the HLB value that an emulsifier should have to be able to stabilise the emulsion can be calculated. However, hydrophilicity is not the only point to consider. The shape of the emulsifier used may be very important as the molecule must fit in the interface (Marszall 1981). Form and required HLB are also related to droplet size. The smaller the droplets are the more convex the interface will be. Thus with smaller droplets, the lipophilic part must be smaller too. The reverse may also be true; if an emulsifier with a higher HLB value -and thus a smaller lipophilic part- is used, a cream with smaller droplets will result.

For optimal stability mixtures of emulsifiers consisting of an hydrophilic emulsifier (high HLB) and a lipophilic coemulsifier (low HLB) are used. Cetostearyl alcohol is one of the most widely used coemulsifiers (e.g. in lanette wax and cetomacrogol wax) because it exists in the α-modification over a wide temperature range. The α-modification is the best stabilizing modification for o/w creams (see chapter 11.1, Nürnberg 1985).

The hydrophilic part of the emulsifier is hydrated, that is, surrounded by water molecules. This causes the hydrophilic part to be much bigger than expected. If temperature rises, this hydration will diminish, the hydrophilic part will become smaller and HLB and emulsifying efficacy are affected. High temperatures may result in separation of the cream. The temperature at which this happens is called the phase inversion temperature. Very strongly hydrophilic emulsifiers, such as sodium laurylsulphate, do not show phase inversion at normal temperatures (below 100°C) (Shinoda and Saito 1969; Lissant 1974; Enever 1976).

At higher temperatures other stability problems may play a role. A cream has many different phases, such as different gel phases, and gel/sol transitions may result in rheological changes. This may cause (or enhance) creaming tendency. Creaming as well as separation results in inhomogeneous creams. Creams should thus be mixed or stirred if they have been exposed to high temperatures. Our basic cream was stable at 45°C for 3 months and at 70°C for 2 weeks. At 70°C some creaming occurs, but this is a slow process (Bakker 1988). Evaporation at these temperatures will be a problem, thus package must be impermeable for water or water vapours.

Because of the high hydrophilicity of lanette wax (sodium laurylsulphate 10% and cetostearyl alcohol 90%) and the high thermostability of creams prepared with these emulsifiers lanette wax is most appropriate. Irritation may develop more rapidly than with cetomacrogol creams, but is uncommon. Incompatibilities of drugs form a more severe problem with cetomacrogol wax than with lanette wax, as many phenolic compounds that are essential drugs (salicylic acid, dithranol and others) are incompatible with cetomacrogol.

3.6 preservation

Oil in water creams are microbiologically vulnerable. Water forms a continuous phase and micro-organisms may spread throughout the cream. Water and nutrients are available. Some micro-organisms can use cetostearyl alcohol as a nutrient and creams may be good growth promoting media. Collapsible tubes would be good packages to prevent contamination, but these are less suitable for tropical use as they are expensive and for single use only, and con-

tents cannot be stirred if necessary. Jars offer only poor protection against contamination. Creams should thus be adequately preserved. Only a few preservatives are appropriate. The main problems are inactivation of preservatives and side effects due to preservatives.

3.6.1 inactivation of preservatives

Various constituents of the cream or package may inhibit preservative activity. Only unbound preservative dissolved in the water phase is active. Partition, adsorption and dissociation thus are inactivating processes. Other inactivating processes are degradation and precipitation.

Partition between the oil and the water phase depends on the solubility of the compound in oil and in water. Paraffins are poor solvents for most preservatives and partition will not be a problem if these are used. Good solvents, generally oils and waxes, should be avoided. Patel and Romanowski determined partition coefficients (concentration in oil/concentration in water) for various systems. They found for methylparaben 0.03 for paraffine/water and 60 for castor oil/water (Patel and Romanowski 1970). Partition coefficients determine relative concentrations. The actual concentration in the aqueous phase is also determined by the amount of lipid present (Patel and Romanowski 1969, 1970; Van Doorne and Dubois 1980). Solubility and thus partition is dependent on temperature. Partition coefficients rise with increasing temperature, active concentrations will thus be less at higher temperatures (Van Doorne and Dubois 1980).

Emulsifiers may inhibit preservatives by two mechanisms; molecular adsorption and partition into micelles. A distinction between the two is not always possible, but may be useful to enable the prediction of the influence of temperature. Inactivation caused by adsorption will be less at higher temperatures but inactivation caused by partition will be higher (Patel 1967; Patel and Romanowski 1970; Kazmi and Mitchell 1971). Nonionics like cetomacrogol are more potent inactivators than anionics like laurylsulphate (Blaugh and Ahsan 1961; Patel 1967; Kazmi and Mitchell 1971). Preservative inactivation by emulsifiers may be very effective, hence the use of Tween 80 in microbiology.

Acid preservatives are only active in the undissociated form. This implicates they should only be used over a small pH range (sorbic acid below pH=5, phenol below pH=9.5). In addition the pH influences the stability of preservatives. The influence of temperature on dissociation is extremely complex. All chemical equilibria will shift with changing temperature, including the dissociation of water and of preservatives. At normal storage temperatures this effect will be small unless appreciable amounts of preservative are already dissociated.

Adsorption of preservatives to solids may play a role (Garrett 1966; McCarthy 1970, 1972; Yousef et al. 1973). Most creams will not contain large amounts of solids but adsorption to packaging materials may be a problem. Absorption will be less at higher temperatures and therefore this will not be a problem specific for tropical climates.

Instability and decomposition may cause inactivation of preservatives. pH may be an important determinant of degradation, as well as temperature. Package materials may influence decomposition (McCarthy 1970, 1972). Degradation will be quicker at higher temperatures (see chapter 12.1). Not only inactivation may be a problem, but toxic degradation products too.

Temperature has a strong influence on various inactivation mechanisms, but also on intrinsic activity. Intrinsic activity will be higher at higher temperatures. The overall effect of all these changes on the total activity is very difficult to predict. It may be expected that in most cases enhanced activity will compensate for enhanced inactivation (Van Doorne and Dubois 1980).

3.6.2 side effects due to preservatives

The most frequent side effects of preservatives are sensitization and irritation. Risk estimation is possible, but will generally be based on the number of side effects reported in literature. The frequency of use must be taken into account as this is a major factor determining the number of side effects reported. Methylparaben has long been considered a notorious sensitizer, but de Groot considers its use relatively safe (de Groot 1988).

It has been reported that black skin is less vulnerable to sensitization than white skin. This has been demonstrated for a limited number of chemical substances but could not be proved for many others. Black skin is as thick as white skin but the horny layer consists of more cell layers, and hence might be more resistant to irritation. The differences may be expected to be the greatest for irritating chemicals. Some authors however argue that the supposed difference does not exist at all, they explain the results of various tests by pointing out the difficulty of

detecting minimal redness of the skin of black people (Anderson and Maibach 1979; Wedig and Maibach 1981).

3.6.3 the choice of a preservative

There are many preservatives for use in dermatologicals and cosmetics. Parabens are the most widely used. In choosing a preservative the main points to consider are intrinsic activity (broad spectrum, lack of resistance), compatibility with the cream system, lack of side effects (toxicity, irritation, sensitization), and stability.

The emergence of bacterial resistance may be a problem but this is very difficult to predict. Resistance may develop if a preservative is used on a large scale, and the more it is used, the more resistance may be reported.

Some drugs may be used as a preservative and as an antiseptic, such as chlorhexidine. Although this may be convenient because only one basic material is needed this is not a good practice, as resistance problems may be more serious.

Cathionactive preservatives (cetrimide, benzalkonium chloride) show various incompatibilities with the systems to be preserved (e.g. Lanette wax) and can better be avoided. Sorbic acid may be irritating, it is only active at pH below 5 and is unstable (see chapter 12.7), but compatible with most cream systems. Various phenolic compounds (e.g. chlorocresol) are generally less well tolerated and not very stable (see chapter 12.6). Mercury compounds are considered obsolete for the use in creams because they are too toxic.

Propylene glycol is compatible with most cream systems and may be universally used as a preservative. In the concentration that is generally used it is well tolerated but at higher concentrations it may be irritating. Propylene glycol is stable. It may enhance the penetration of various drugs (e.g. corticosteroids). Preservation with propylene glycol is quite expensive as high concentrations are needed (10%).

Methylparaben seems to be the best choice. It is reasonably stable, though hydrolysis does occur (see chapter 12.2), it has a good activity and it is well tolerated. It is compatible with our basic cream, but not with creams that contain vegetable oils (Van Doorne and Dubois 1980). It is perhaps the most widely used preservative in dermatologicals and cosmetics, hence its side effects and other properties are very well documented. Sensitization may occur but is not very common with the concentrations generally used (de Groot 1988). It may be used over a large pH range, but stability is best at pH 4 to 5 (see chapter 12.2). Methylparaben is cheap, especially if the concentration needed is taken into account.

3.7 preparation methods

The preparation method used is one of the various factors determining the stability of a cream. Crystallization of the emulsifier is influenced by the cooling rate, the droplet size by the mixing efficiency and the mixing temperature. Cold emulsification may lead to a homogeneous emulsion, but such an emulsion may be less stable. If the cream is not well stirred during cooling, a less stable cream will result (Bakker 1988). Care should thus be taken that the preparation method used ensures a stable product. Recipes given in most formularies, and in ours too, are generally developed for small scale preparation. If preparation is scaled up, for example to a production capacity of 10 kilograms, both the mixing efficiency and the cooling rate can be affected. If production is done on a larger scale, it is necessary to check whether the resulting creams are stable enough.

3.8 conclusions

A simple and stable cream for tropical use can be obtained with the following formula: lanette wax SX 15%, paraffine 35%, methylparaben 0.15%, water to 100%. Other preservatives that may be used but are less appropriate are sorbic acid (unstable!) and propylene glycol (expensive!).

The cream must be packed in a package which allows stirring of the contents but prevents evaporation of water. After prolonged storage, or after storage at high temperatures (transport) creams should be stirred before they can be dispensed or used.

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4 Shake lotions

4.1 introduction

Shake lotions are lotions that contain a certain amount of powder. Only the type of shake lotion that consists of a powder and a water phase is discussed here. After applying the lotion on the skin the water will evaporate, which results in a cooling effect. The powders in the lotion may enhance this effect by enlarging the surface area from which evaporation takes place. Shake lotions have general soothing and weak astringent properties. Various drugs may be added, but we consider only the antipruritic shake lotion essential. Corticosteroids may be added but they are less stable in calamine lotion. Tars can better be prescribed in pastes, creams or solutions.

Calamine lotion is one of the most common lotions and it is considered essential by the WHO. This lotion with 0.5% phenol has very good properties for tropical use. It is stable (microbiologically, physically) and has a cooling, antipruritic, weak astringent and weak antiseptic effect. Other shake lotions, such as Lotio Alba, are microbiologically more vulnerable or contain raw materials that are less appropriate for our purposes. Various common ingredients of shake lotions can better be avoided as they may cause side effects. Talc for example may cause granulomas if used on damaged skin. This is due to crystalline silicates in certain specific modifications that are present in the talc. The same effects can be caused by other silicates such as asbest. Natural clays like bentonite do not contain these modifications and in this aspect they are safe (Deichmann and Gerarde 1969). Starch can better be avoided as it is often contaminated with micro-organisms (see chapter 11.2). Zinc may be absorbed from wounds (Hallmans 1978), but the relevance of this effect in clinical practice is questionable (Brüske and Salfeld 1987). If used on large parts of the body or on damaged skin phenol may also be absorbed. This may result in systemic side effects. Thus calamine lotion should not be used on open wounds.

4.2 composition of calamine lotion

According to the British Pharmacopoeia (and various other pharmacopoeias) calamine lotion contains per 100 milliliters: calamine 15 grams, zinc oxide 5 grams, veegum 3 grams, sodium citrate 0.5 grams, glycerine 5 milliliters, liquified phenol 0.5 milliliters and water. Some of these ingredients are essential whereas others may be substituted for cheaper ones.

According to the British pharmacopoeia, calamine is basic zinc carbonate with 2% ferrous oxide, but according to the United States Pharmacopoeia it is zinc oxide with 2% ferrous oxide. The two are considered equivalent. Ferrous oxide colours the mixture to match the colour of white skin. This makes the preparation cosmetically very acceptable. But for dark coloured people, this colouring agent is not adequate. Zinc oxide may be used instead of calamine without affecting the properties of the lotion.

Veegum is, in contrast to bentonite, a standardised preparation. Bentonite may be used instead because the quality of the bentonites currently marketed for pharmaceutical use is adequate. Glycerine is needed for the trituration of the bentonite and zinc oxide. When highly efficient mixers are available, glycerin can be left out. But this will usually not be the case in small scale production units in tropical countries. So we consider this an essential ingredient. Sodium citrate controls flocculation in the suspension system and is essential to obtain a stable and pourable suspension. The trisodium citrate is used for this purpose. Other citrates may be used but they may enhance dissolution of zinc oxide (Fenton 1962; Wood et al. 1962; Anderson and Hill 1963; Berg 1966). Whether this is a problem in clinical practice is not clear. The trisodium salt is used for oral rehydration also, so it seems best to stick to this specific salt.

We thus consider the following formula for calamine lotion most appropriate: zinc oxide 20 grams, bentonite 3 grams, sodium citrate 0.5 grams, glycerin 5 milliliters, liquified phenol 0.5 milliliters and water to 100 milliliters. Although this preparation contains no calamine we want to stick to the name of the lotion, as it is generally used. It may be called modified calamine lotion to indicate it is not the same as the calamine lotion of the British pharmacopoeia, United States Pharmacopoeia, or any other.

4.3 sedimentation

Most pharmaceutical suspensions will separate during storage (sedimentation). Thus it is necessary to control this process. Sedimentation, if it occurs, must be slow and resuspending the sediment must be easy.

Sedimentation depends mainly on the difference in specific gravity of the particles and the fluid phase, the size of the particles and the rheological properties of the fluid phase. Sedimentation is slower when:

a) the particles are smaller;
b) the difference in specific gravity is less; or
c) the viscosity of the liquid phase is greater.

It is possible, at least theoretically, that there is no difference in specific gravity. In this case there is no driving force for sedimentation and the suspension will be physically stable for an indefinite time. The resuspendability depends mainly on how the suspended particles are packed. The bigger the particles, the looser the sediment and the better the resuspendability.

The particles may associate (flocculate) to form bigger clusters. These clusters may sediment more rapidly, but they are easier to resuspend. In the formulation of pharmaceutical suspensions controlled flocculation is often used as a means to control sedimentation and resuspendability, and this is also true for our modified calamine lotion. Sodium citrate acts as a partial deflocculating agent. The viscosity of the liquid phase is increased by the bentonite that also enhances, to some extent, the resuspendability (Fenton 1962; Wood et al. 1962; Anderson and Hill 1963; Berg 1966).

From the results of our experiments (see addendum B) it may be concluded that the sedimentation is somewhat faster at higher temperatures, but still very slow, and that the resuspendability remains good. We thus conclude that modified calamine lotion is physically stable under tropical conditions.

4.4 preservation

Modified calamine lotion is preserved with phenol (that has, in addition, antipruritic and antiseptic properties). The high pH of the lotion and the presence of large amounts of solid matter with a high absorptive power (bentonite) prohibits the use of most other preservatives. Three mechanisms may decrease the preservative activity of phenol: dissociation, adsorption and degradation (see chapter 12.6).

Only undissociated phenol is active (Garrett 1966). The pH of modified calamine lotion is 9.1; for other calamine lotions values up to 9.5 have been reported. At 20°C and a pH of 9.1 85.5% of the phenol is nondissociated, at pH 9.5 this is 71.1%. The influence of temperature is difficult to predict, but will be limited. At a pH of 9 to 9.5 some bacteria are still viable, but at higher pH values bacterial growth will not be a problem (Schlegel 1981). Phenol is thus adequate for the preservation of aqueous solutions with these high pH values.

Adsorption to particles may be an important inactivation mechanism for preservatives. Bentonite is a good absorbent for preservatives, but more specifically for cathionic substances. Adsorption will be less at higher temperatures, it is not a tropical problem. We determined the adsorption of phenol to the powder phase of the lotion. Adsorption was practically nonexistent (see addendum C). Adsorption is thus not likely to be a problem.

Liquified phenol is preferred, this is more easy to process than pure phenol. It contains approximately 80 to 90% phenol. Resulting free concentrations of nondissociated phenol in the lotion will thus not be lower than 0.3%, this is considered appropriate.

4.5 conclusion

The suggested formulation for calamine lotion is appropriate for tropical use. It is cheaper than the original formulation of the British Pharmacopoeia and other pharmacopoeias, but it has the same therapeutical properties. The original formulation may also be used. Preservation is adequate.

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2 Stability of drugs

1 Introduction

1. 1 chemical stability: reaction kinetics

The activity of a drug may decrease in the time due to degradation of active ingredients. The relation between concentration and time is characterised by two parameters: the order of the reaction and the reaction rate constant. The order of the reaction describes the shape of the concentration-time curve (see figure 12.1), the reaction constant defines the slope of the curve.

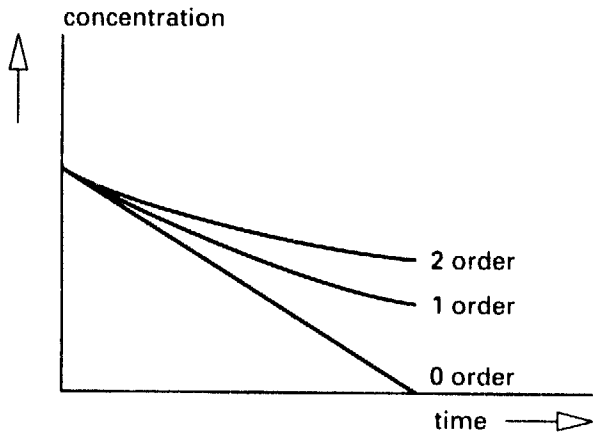

figure 12.1:
the relation between concentration and time for zero- first- and second order reactions.

Degradation can be described by the general formula I. The reaction rate can be described by the general formula II.

$$aA + bB \longrightarrow cC + dD \qquad I$$

$$v = k[A]^a . [B]^b \qquad II$$

$$n = a + b \qquad III$$

A, B = reactants
C, D = products
[x] = concentration of x
v = reaction rate
k = reaction rate constant
n = order of reaction

If the the reaction rate is independent of the concentration of reactants, the reaction is zero order. In this case the reaction rate is independent on the time. If the reaction rate is directly proportional to the concentration of reactant, the reaction is first order. In second order reactions the reaction rate is directly proportional to the square of the concentration of reactant. Higher orders are also possible. If the reaction equation is known, the order of reaction can be determined with formula III. The order of reaction is independent on temperature, at least within a certain temperature range. Pseudo zero order reactions are described adequately by zero order reaction kinetics, but this is not the real order of reaction. This can for example be the case if the

solubility of the primary reactant limits the reaction rate.

The reaction rate constant determines the slope of the concentration/time curve. It is a measure for the reaction rate.

If the order of the reaction and the reaction rate constant are known, the degradation in a given time may be calculated. The following formula are used:

$$k = \frac{[A]_0 - [A]_t}{t} \qquad IV$$

$$k = \frac{\ln [A]_0 / [A]_t}{t} \qquad V$$

k = reaction rate constant
[A]o = original concentration
[A]t = concentration remaining
t = time

Formula IV should be used for zero order reactions, formula V for first order reactions.

In industry, shelf lives are generally calculated from data obtained at higher temperatures. It is possible to calculate the reaction rate constant at a different temperature with the Arrhenius equation (formula VI)

$$k = A.e^{-Eg / R.T} \qquad VI$$

k = reaction rate constant
Ea = activation energy
R = 8.314 J/mol.K
T = absolute temperature (K)
A = frequency factor

A and Ea are approximately constant over a limited temperature range. If these are known, or if reaction rate constants at two temperatures are known, the reaction rate constant at a given temperature can be calculated (Connors et al. 1979).

In many cases a number of consecutive reactions are involved in degradation, and the only reaction parameters known are those of the overall reaction. These are called "observed" or "apparent" .

1. 2 chemical stability: shelf life

Shelf life is usually defined as the time during which the preparation complies with the pharmacopoeia standards. A practical, but arbitrary limit is that at least 90% of the declared amount of active ingredient should be present in the preparation. In certain specific cases a wider limit may be acceptable. In some other cases shelf life can be prolonged by adding an excess of active ingredient.

The activity of the preparation is not the only point to consider, the toxicity of degradation products should also be taken into account. If toxic degradation products are formed, their no-effect level dictates shelf life. Carcinogens should be absent at all times, because their no-effect level is zero.

The degradation depends on the temperature, therefore the shelf life should always be determined at the actual storage temperature. In order to differentiate between countries with different temperatures the various climates are classified. They are usually classified as follows:

I: temperate zones;
II: mediterranean zones;
III: hot and dry zones;
IV: hot and humid zones.

For the calculation of shelf lives some kind of average temperature should be determined. Haynes introduced kinetic average temperatures, also called virtual temperatures (Haynes 1971). The idea behind this system is the following: assuming that there is no temperature control, temperatures in storage places are changing constantly. To calculate a shelf life, one could use the maximum temperature. If this is done, the calculated shelf life will be very short. One could also use a simple average temperature for the calculation of shelf lives. However, because the relation of degradation with temperature is a very complicated one, this is neither appropriate.

Degradation after one month's storage 20°C and one month's storage at 40°C is not the same as degradation after two months' storage at 30°C. Shelf lives based on average temperatures tend to be too long and limits will be unsafe. The kinetic average temperature, that Haynes determined, can be used to overcome this problem. Degradation rates at the kinetic average temperature are the same as degradation rates at the real pattern of temperatures (Haynes 1971; Grimm 1975).

The calculation of kinetic average temperatures is very complicated. Fortunately, Haynes could demonstrate that kinetic average temperatures for a certain climate could be used worldwide in all climates with the same classification, and for all drugs. Kinetic average temperatures are dependent on activation energy, which is characteristic for a certain drug, but the maximum error due to differences between drugs was only 1°C (Haynes 1971).

In most climates the temperature pattern is not constant. There are cooler and hotter months. If a drug can only be stored for a month this could be the hottest one. For drugs that can be stored for years, an yearly average can be taken. Therefore, kinetic average temperatures are dependent upon storage times. Grimm calculated kinetic average temperatures for climates III and IV for different times of the year. During eight normal months the kinetic average temperature was 27°C, during three hot months it was 34°C and during the hottest month it was 40°C. Over one full year the kinetic average temperature was 31°C. This was raised to 33.6°C after transport under extreme circumstances or to 32.4°C over two years after transport. These values are calculated assuming that the activation energy is 20 kcal/mol; for chemicals with a high activation energy of 30 kcal/mol the error is only 0.5°. Grimm's calculations are based on extremes and may be considered safe for worldwide use.

In the calculation of shelf lives, kinetic average temperatures reflecting the actual shelf life should be chosen. If stability is poor (about one month) the kinetic average temperature is 40°C, if it is about three months it is 34°C (both after cooled transport only). If stability is about a year the kinetic average temperature is 33.6°C and transport without special cooling facilities is possible.

Calculation of shelf lives remains very difficult or even impossible as in most cases not all reaction parameters can be adequately defined.

1. 3 physical instability of raw materials

A wide variety of physical processes is likely to affect the quality of stored raw materials or preparations. Adequate packaging is very important. This may in most cases limit the loss of ingredients. For quick reference to physical stability of raw materials table 12.5 in section 9 of this chapter contains a summary of problems concerning physical stability. Problems most likely to be encountered are:

* Evaporation depends on many parameters. Temperature and air movements ('wind') are the most important environmental (extrinsic) factors. Evaporation is a reversible process, in a well filled, airtight container it will only lead to a minimal loss of ingredients. Evaporation losses may occur from containers that cannot be closed airtight.
* Melting is, like evaporation, a reversible process. If the preparation is adequately packed, it will not result in a loss of ingredients. Materials with a melting point below 70°C should never be packed in paper or plastic bags. After resolidification the particle size will be different and polymorphic changes may occur.
* Crystallization at low temperatures may occur. This will not occur at higher temperatures and is therefore not a tropical problem. If it happens, heating the material will solve the problem. If crystallization is expected, the product or the raw material should be heated and mixed before using it.
* Hygroscopicity (absorption of moisture from the environment) may be a serious problem as secondary processes may lead to a loss of ingredients or material. These secondary processes include microbial spoilage and chemical degradation. For some materials dissolution in absorbed water is possible. After this has occurred processing may be difficult. It is very difficult to prevent absorption of moisture. The materials should be kept in airtight containers at all times.

1. 4 microbiological stability

Micro-organisms need water to grow. In the absence of water some organisms are able to remain viable for long periods of time (not only sporeforming organisms). This has for example been observed in various oils by Myers (Myers 1969). Microbial spoilage is not likely to occur when no water is present. In the presence of water it can be prevented by preservation methods.

Some raw materials may contain large numbers of micro-organisms, due to either preparation methods or provenance of the material. If brought in a favourable environment these micro-organisms may start growing and spoiling the material. This may be a secondary process after absorption of moisture from air, as has been shown for starch (Bos et al. 1989), or it may occur after processing these materials.

Bentonite may be heavily contaminated with micro-organisms. This is caused by the methods used in the preparation of the raw material. Water may also be heavily contaminated. To overcome this problem all water used for the preparation of dermatologicals should be boiled before use. Some of the raw materials have an antimicrobial effect themselves.

1. 5 package and stability

Package design and packaging materials play a crucial role in drug stability. This is mainly because the package can protect the preparation from adverse environmental conditions. For the chemical stability, protection against humidity, oxygen and light is most important. For the physical stability, the water vapor- and gas permeability may be important, as well as the integrity of the package and the container design. For microbiological stability, the integrity of the package and the container design are most important.

To protect a substance adequately, the packaging material has to be chosen carefully. But integrity of the package (cracks) and tightness of the closure are just as important. Another important factor to consider is the weight of the material because this is a major determining factor in transport costs. The cost of the materials and the container production also plays a role, as does possibility to reuse the package. The costs and the reusability should be evaluated in relation to each other. Of course, the local situation should be considered too. This local situation determines whether deposit systems can work. A final point to consider relates to environmental hazards due to discarded packaging materials. Table 12.1 summarizes the properties of some container materials.

table 12.1:
properties of a number of packaging materials. + indicates desirable properties, - undesirable properties.

material	permeability			weight	cost	reuse	environment
	water vapor	oxygen	gasses				
paper	-	-	-	+	+	-	-
glass	+	+	+	-	+	+	+
polyethylene	+	-	-	+	+	+	+
PVC	-	+	+	+	+	+	-

A keen container design is just as important as a good choice for a packaging material. The space occupied by empty containers and the weight of the containers are important in relation to transport costs. Conical containers could be designed so that without closure they can be put into each other. Also, conical containers with a wide opening are easy to clean.

Inhomogeneous preparations have to be stirred before use. This implicates a container with a wide opening should be used for such products. A wide opening is also essential for thorough cleaning of containers that are to be reused. Frequently reopening and stirring of the contents of jars will increase the risk for microbial contamination. Therefore we have selected preparations with a good physical and microbial stability. However, some physical instabilities can not be avoided and stirring should be possible for a number of preparations.

The closure should be designed so that it fits tightly, but it should not be too difficult to open. Collapsible tubes are not appropriate as they do not allow stirring of the contents. Another problem of collapsible tubes is that it is not possible to check the homogeneity of the contents.

A good choice for the packaging of dermatological preparations could be:
1. coloured glass bottles for fluid preparations;
2. polyethylene jars of conical shape with a wide opening for semisolids (glass can be used instead, but this is a little more expensive and heavier);
3. glass jars for a limited number of semisolid preparations that cannot be packed in the polyethylene jars (zinc oil and dithranol preparations).

1.6 literature

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2 Hydrolysis of benzoic acid esters

2. 1 introduction

Benzoic acid esters are often used in dermatological preparations. The compounds that are relevant to this book are the preservative methylparaben and the scabicide benzylbenzoate (see figure 12.2).

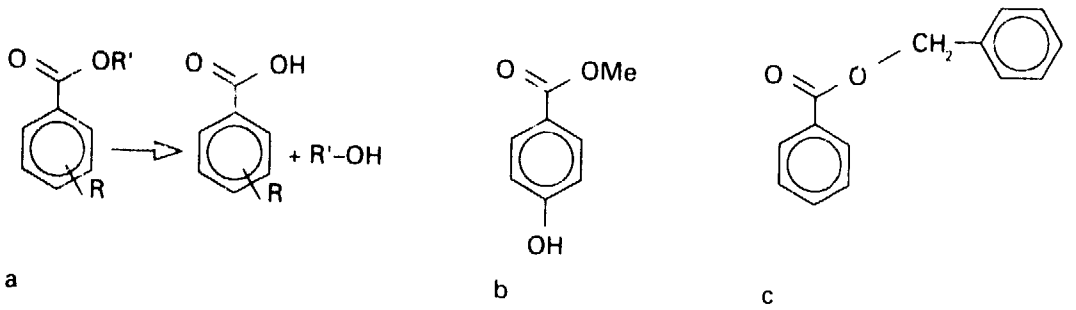

figure 12.2:
hydrolysis of benzoic acid esters (a); molecular formula of methylparaben (b) and of benzylbenzoate (c)

2. 2 reaction mechanism

In the hydrolysis of benzoic acid esters various mechanisms are involved, depending on the reaction medium and the substituents R and R'. Hydrolysis may be acid or base catalyzed. It may result from a nucleophilic substitution of OR' by OH (Sn2), from separation of a R'+ carbonium ion (Sn1), or other mechanisms. The reaction mechanism depends mainly on the R' substituent, the R substituent influences the reaction kinetics to some extent, but has little influence on the reaction mechanism (Gould 1959).

The effect of substituents on the reaction rate can be quantified by means of the Hammett-Taft equations. To do this, many parameters must be known. It is therefore not generally feasible (Hancock and Falls 1961; Washkuhn et al. 1970; Johnson 1973).

2.3 stability of the parabens

Parabens are hydroxybenzoic acid esters and are degraded by hydrolysis. This results in an alcohol (methanol, ethanol, propanol) and hydroxybenzoic acid. These products are relatively nontoxic, the main problem is a reduction of activity. Various authors determined the reaction kinetics at different pH values and temperatures (Raval and Parrott 1967; Kamada and Yata 1973; Blaug and Grant 1974; Sunderland and Watts 1984). The reaction was strongly dependent on the pH. The reaction was of (pseudo) first order at all pH values measured, but the activation energy was dependent on pH; this may reflect different reaction mechanisms at different pH values. The Hammett-Taft equation could not be used with the parabens; this was most probably due to the effect of pH on the electron activity of the para hydroxy group (Sunderland and Watts 1984).

The reaction rate constants determined by Sunderland and Watts for methylparaben are consistent with other values reported in literature (Raval and Parrott 1967; Kamada and Yata 1973; Blaug and Grant 1974; Sunderland and Watts 1984). On the basis of these constants we calculated shelf lives (90% remaining) for methylparaben at different pH values for climates III or IV in the presence of water (table 12.2). The values at pH 4 to 5 are poorly reproducible; this is due to difficulties encountered in measuring extremely slow reaction rates (Kamada and Yata 1973; Sunderland and Watts 1984).

table 12.2:
stability of methylparaben (based on Sunderland and Watts 1984). (Teff.= kinetic average temperature; Kobs.=apparent reaction rate constant; d=day; y=year).

pH	Teff.	Kobs (/d)	shelf life	
1.26	40 °C	$6.8\ 10^{-3}$	16 d	
2.26	33.6 °C	$3.0\ 10^{-4}$	355 d;	1.0 y
2.56	33.6 °C	$1.4\ 10^{-4}$	757 d;	2.1 y
3.82	33.6 °C	$7.3\ 10^{-6}$	14376 d;	39.4 y
4.31	33.6 °C	$6.7\ 10^{-6}$	15702 d;	43.0 y
4.74	33.6 °C	$1.3\ 10^{-5}$	8309 d;	22.8 y
5.89	33.6 °C	$9.6\ 10^{-5}$	1098 d;	3.0 y
6.58	33.6 °C	$4.8\ 10^{-4}$	218 d;	0.6 y
7.67	40 °C	$4.1\ 10^{-3}$	26 d	
7.93	40 °C	$5.2\ 10^{-3}$	20 d	
8.76	40 °C	$1.2\ 10^{-2}$	9 d	

It may be concluded from these values that methylparaben is stable at pH values of 3 to 6. The reaction parameters for propyl- or ethyl- paraben are comparable to those of methylparaben. Basic cream is slightly acidic and methylparaben is stable in this preparation. Because methylparaben has a good activity in basic cream and is generally well tolerated, it is an appropriate preservative for basic cream. The parabens are even more stable if contact with water is avoided. Raw materials may be stored for long times if they are properly packed. Parabens are not suitable for preservation of shake lotions with an alkaline pH like calamine lotion.

2. 4 stability of benzylbenzoate

Benzylbenzoate degrades to benzoic acid and benzyl alcohol. These are less active against scabies mites. The degradation products of benzylbenzoate are relatively nontoxic. Baker and coworkers found low contents of benzylbenzoate in some emulsions (formulated according to the British Pharmacopoeia). They found only minute amounts of the degradation products. They thought that these low concentrations of benzylbenzoate were not due to degradation but to partial separation of the emulsion at the time of dispensing (Baker et al. 1967). Benzylbenzoate emulsion should be well mixed before use or before dispensing. Hydrolysis of benzylbenzoate in emulsions is to be expected, but will be limited as contact with water is limited. The only possible contact of benzylbenzoate is at the interface, benzylbenzoate is not dissolved in the water. The emulsion can therefore be stored for longer times. However, because of physical and microbial stability, we recommend to use it within three months after production. The raw material is stable if contact with water is avoided.

2. 5 literature

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3 Stability of chlorhexidine in solutions

3. 1 introduction

Chlorhexidine solutions are used on a large scale throughout the world. Hydrolysis of the compound is to be expected. Chlorhexidine is usually marketed and stored in stock solutions, the digluconate salt is not even available as a preparation that contains no water. It is therefore important to know if, and if so, how fast hydrolysis occurs.

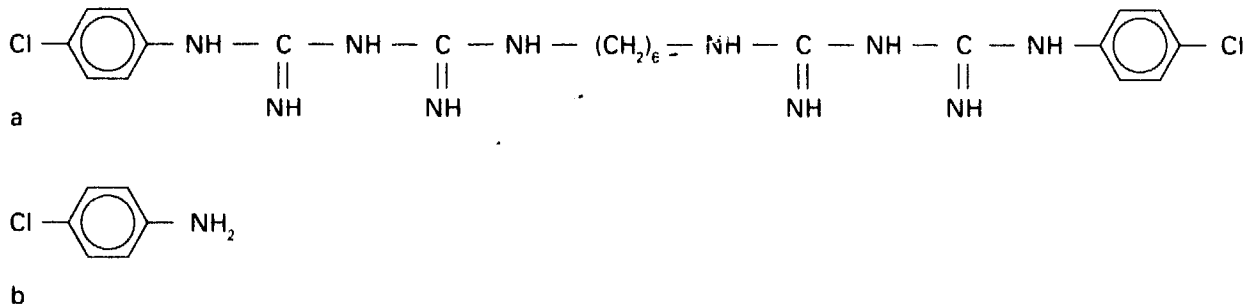

figure 12.3:
hydrolysis of chlorhexidine (chlorhexidine: a, parachloraniline: b)

3. 2 degradation products

Chlorhexidine degrades by hydrolysis. Various anilines are formed. One of the major products is parachloraniline (Goodal et al. 1968; Dolby et al. 1972). Chloranilines are toxic substances that may be absorbed through the skin (Sax 1968; Bretherick 1981). Chloraniline induces methemoglobinemia (Dreisbach 1971; Verberk and Zielhuis 1980) but in adults this effect is insignificant with doses lower than 0.5 gram a day (Goodal et al. 1968). Chloranilines were once associated with cancer. Cancer of the bladder was the most common. Anilines are excreted by the kidneys and thus concentrated in urine. Carcinogenicity is now attributed to byproducts generally found in commercial anilines used in industry, but not to the chloranilines. Suspected carcinogens should not be present in any compound used for the preparation of drugs. It is impossible to determine a no effect level for this class of toxic substances. The presence of chloraniline in chlorhexidine is limited by the British Pharmacopoeia to 500 ppm relative to chlorhexidine. This limit is a reflection of the requirements on the production processes and the purity of chlorhexidine rather than a safe level. If chloraniline is a suspected carcinogen, this is far too high, if it is a toxic substance (methemoglobinemia) it is unnecessarily low.

3. 3 reaction kinetics

Chlorhexidine is most stable at pH values of about 6, hydrolysis increases at higher or lower pH values (Dolby et al. 1972). Degradation due to sterilization may be appreciable, cloraniline contents after sterilization usually exceed the British Pharmacopoeia limit of 500 ppm (Goodal et al. 1968; Dolby et al. 1972). In the literature various reaction parameters have been reported, both at sterilization temperatures (Goodal et al. 1968; Jaminet et al. 1970; Dolby et al. 1972) and at ambient temperatures (Goodal et al. 1968; Grimm et al. 1973; Pauwelczyk and Plotkoniak 1976; Løberg and Hegna 1979; Kucharski et al. 1981; Fiumano et al. 1983). These are usually determined at one temperature only, and in different, poorly specificated preparations (e.g. without specification of the pH). It is very difficult to use these parameters for an accurate calculation of shelf life. Some reaction rate constants are summarised in table 12.3, together with the shelf lives that can be calculated from them using the limit of the British Pharmacopoeia of 500 ppm chloraniline or a 10% degradation limit.

table 12.3:
shelf lives of chlorhexidine solutions (pH values not specified).

temperature	t 500ppm (days)	t 90% (days)	k (per day)	reference
?	6	270	$3.9\ 10^{-4}$	(Pauwelszyk)
20 C	3	135	$7.8\ 10^{-4}$	(Kucharski)
25 C	35	1471	$7.2\ 10^{-5}$	(Grimm)
35 C	15	645	$1.6\ 10^{-4}$	(Grimm)
45 C	7	298	$3.5\ 10^{-4}$	(Grimm)

Degradation was found to follow first order kinetics (Grimm et al. 1973) and was accelerated by light (Kucnarski et al. 1981). Reported values are within the same range, except the very fast degradation reported by Fiumano and coworkers (Fiumano et al. 1983), but they determined remaining chlorhexidine in the presence of chlorides. Chlorides are incompatible with chlorhexidine in solutions containing 0.5% or more of chlorhexidine. The concentration of chlorhexidine in the experiments of Fiumano and coworkers was not defined in the available abstract.

The values in table 12.3, as well as other kinetics reported, are determined in diluted solutions. Whether the reaction rates are the same in concentrated solutions is uncertain. The only conclusion that can be drawn on the basis of this information is that degradation of chlorhexidine may be a problem.

Raw materials are likely to be kept in stock for longer periods than preparations. Chlorhexidine is more stable if it is kept free from water. Chlorhexidine digluconate can not be kept free from water, because it is only available as a solution. The diacetate salt however is available as crystals. It is expected that these diacetate crystals have a far better stability than the digluconate solution. Chlorhexidine diacetate is as active as chlorhexidine digluconate, but its solubility in water is less (1.5%w/v). This solubility is just high enough to prepare chlorhexidine solutions of the required strength (1%w/v). The diacetate however is not as widely used as the digluconate. The choice for either the digluconate or the diacetate must be made locally, considering the required storage times and the local storage conditions.

3. 4 literature

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4 Stability and formulation of dithranol

4. 1 introduction

Dithranol is a very reactive substance. It is unstable. Various components of vehicles in general use affect the stability of dithranol. These relative incompatibilities make special precautions necessary, such as the addition of stabilisers. This is especially important for tropical countries.

4. 2 reaction mechanism

The degradation reaction of dithranol is oxidative. Free radical mechanisms play a role. Radical initiators catalyse degradation reactions. Reaction leads, probably via oxygen radicals, to 1.8-dihydroxyanthraquinone and 1.8.1'.8'-tetrahydroxydianthron (see figure 12.4). The hydroxy groups at the positions 1 and 8 may also be attacked. This will result in polymerization products (Whitefield 1981; Sa e Melo et al. 1983). It is still not certain if degradation products play a role in the therapeutic activity or side effects. Some degradation products have a biological activity. For example anthralin brown was shown to influence the activity of glucose-6-phosphate-dehydrogenase (Jucklin 1981; Cavey et al. 1982). The risks associated with the use of partially degraded dithranol preparations are still impossible to asses.

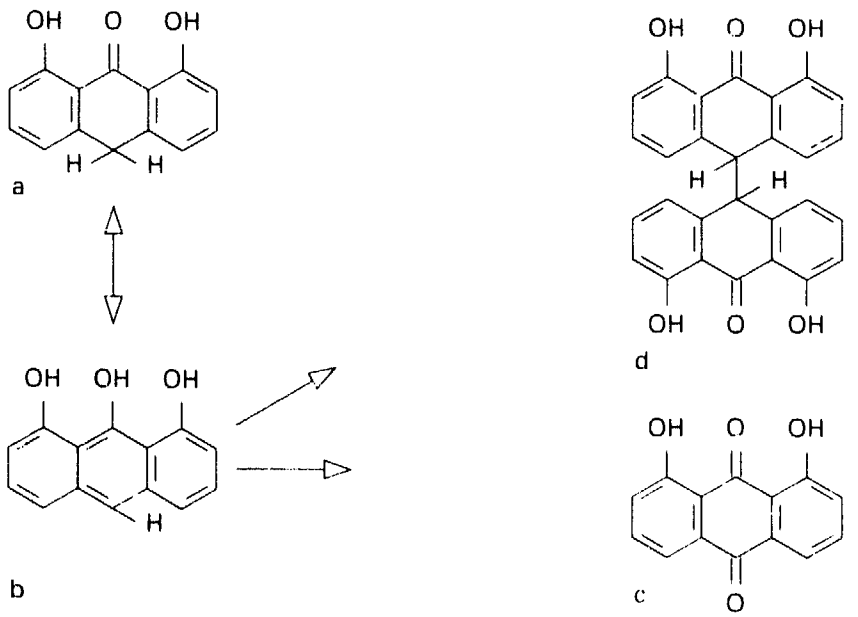

figure 12.4:
degradation of dithranol (a, b) to 1.8-dihydroxyanthraquinone (c) and 1.8.1'.8'-tetrahydroxydianthron.

4. 3 reaction kinetics

In literature no quantitative reaction parameters have been reported that can be used for the calculation of shelf lives. For most drugs degrading by oxidation, hardly any reaction parameters have been reported because degradation depends on too many variables to make general calculations feasible. Some qualitative remarks can be made on dithranol:

* At higher pH values degradation is increased. Dissociation seems to play a role; this is consistent with the fact that the more acidic hydroxy group at position 9 is attacked first. Polymerization reactions are fast at highly alkaline pH values. This explains why colouration of skin, clothing and bedding is more pronounced if alkaline soaps are used in washing (Van Scott and Yu 1981).
* Oxygen radicals play a role in the initiation of the degradation reaction. Exclusion of oxygen (airtight packaging or packaging under nitrogen) will slow down degradation but will not prevent it (Whitefield 1981; Sa e Melo et al. 1983).
* Light may increase degradation.
* Dithranol bound to protein is rapidly degraded (Sa e Melo et al. 1983). Whether this plays a role in the mode of action of dithranol is still not known.
* Zinc oxide increases degradation. This may be prevented by adding salicylic acid (2%). Whether this is due to alkaline impurities or to trace amounts of radical initiators such as peroxides or heavy metals is unclear.

4. 4 stability of dithranol in preparations

In the absence of light, oxygen or catalysts (radical initiators like peroxides and heavy metals) dithranol is fairly stable (Whitefield 1981). In most preparations dithranol must be stabilised. Only in petrolatum or ambiphilic creams dithranol need not be stabilised.

Zinc oxide containing preparations may be stabilised with 2% salicylic acid. Salicylic acid is also an appropriate stabiliser for dithranol in fatty ointments. Creams can be stabilised with ascorbic acid. Dithranol is soluble in lipids, but not in water. Ascorbic acid on the other hand is soluble in water, but not in lipids. Dithranol in the inner (lipid) phase is adequately isolated from air by a low oxygen containing aqueous phase (Seville et al. 1979; Whitefield 1981). Dithranol in petrolatum need not be stabilised, but salicylic acid may be added for its therapeutic effect.

Although no quantitative data are available (e.g. Seville and coworkers found "little degradation" after 6 months at 24 or 29°C), we estimate the shelf life of adequately stabilised preparations containing dithranol to be at least 6 months if kept below 20°C.

4. 5 literature

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5 Stability of hydrocortisone and other corticosteroids

5. 1 introduction

Corticosteroids can be used in many diseases. For the use in skin diseases special corticosteroids have been developed. These have been made more lipophilic by masking the hydrophilic hydroxygroups at positions 17 and 21 (see figure 12.5a). In this way, the absorption

of the corticosteroid is improved. Ester hydrolysis will thus result in corticosteroids that are less well absorbed.

Degradation reactions may also occur in the steroid skeleton. It depends on the type of steroid and ester, and the reaction environment, which reaction is the fastest. In this section, we will deal with the degradation reactions that occur at the steroid skeleton first. This part deals with the stability of non esterified steroids. Esters may prevent degradation reactions at the steroid skeleton, but this is not a general rule. The second part of this section deals with hydrolysis of esters and acetonides.

5. 2 corticosteroid degradation

Corticosteroid skeletons can be degraded via a great number of reaction mechanisms. For a given steroid, the mechanism depends on the reaction medium. Generally, the side chain at position 17 is the most reactive part of the molecule, but degradation may also occur at the A-ring. In situations usually encountered in practice, degradation at the 17 side chain determines the stability (Hansen and Bundgaard 1979, 1980a).

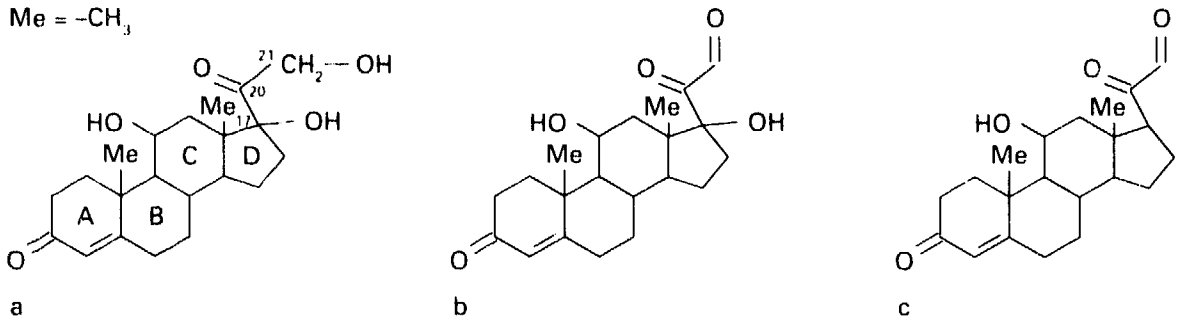

figure 12.5:
molecular formula of hydrocortisone (a); degradation products of hydrocortisone: 21-dehydro-hydrocortisone (b) and 17-deoxy-21-dehydro-hydrocortisone (c)

The remarks made in the following text on hydrocortisone are generally valid for most corticosteroids.

In an acidic reaction medium degradation occurs via a non-oxidative, acid catalysed reaction, resulting in the formation of 17-deoxy, 21-dehydrohydrocortisone (a glyoxal, see figure 12.5c). This reaction is not influenced by heavy metals or oxygen (Hansen and Bundgaard 1980b).

In neutral to slightly acidic media degradation occurs via two competing reactions, the acid catalysed non oxidative reaction described above, and an oxidative reaction resulting in the formation of 21-dehydrohydrocortison (see figure 12.5b) which is also a glyoxal. The latter reaction is influenced by heavy metal traces or oxygen. The glyoxals that are formed are unstable compounds that are further degraded (Bundgaard 1980).

In alkaline reaction media a great number of competing reactions occur, depending on the presence of catalysts, light and pH (Hansen and Bundgaard 1980a). These may or may not be oxidative. Glyoxals may be formed in alkaline media as well.

5. 2. 1 degradation products

Glyoxals may be formed. These are reactive substances, that may react with protein (arginine). This results in a denaturation of the protein involved and may provoke an allergic reaction. This may be the general mechanism involved in corticosteroid allergy (Bundgaard 1980). The incidence of such reactions is very low, but may be underreported since corticosteroids mask allergic responses.

5. 2. 2 degradation kinetics

Generally valid degradation kinetics of corticosteroids cannot be given as degradation depends on too many, often unknown, factors and too many reaction mechanisms are involved. Apparent reaction parameters for overall degradation are a summation of all those separate

reactions. An estimate of the reaction rates can be based on some of these apparent parameters that have been reported in the literature. The degradation of hydrocortisone is pseudo first order at neutral to acidic pH values, but at the start of degradation first order kinetics are not applicable. In alkaline media the order of reaction is unknown (Hansen and Bundgaard 1979, 1980a). In highly acidic media only one reaction is involved (pH<2) and the reaction kinetics may be determined. The activation energy for this reaction was 97.5 kJ/mol (Hansen and Bundgaard 1979).

Some apparent reaction parameters at neutral pH were determined by Hansen and Bundgaard. They found apparent reaction rate constants at 70°C: pH 5.07, Kobs=0.58 10^{-2}/h; pH 7.09, Kobs 6.5 10^{-2}/h. (Hansen and Bundgaard 1980a). Shelf life in aqueous solution at pH 5 may be estimated on the basis of this reaction rate constants, but these estimates are quite inaccurate. These estimates for the shelf life of hydrocortisone are about 250 days at 20°C and 130 days at 25°C. This may be raised to about 160 days at 25°C if sodium edetate is added. Heavy metals increased reaction rates. At 40°C (the appropriate kinetic average temperature) the shelf life of aqueous solutions of hydrocortisone is only some 3 weeks. In alkaline media no reproducible kinetic parameters could be determined. Hydrocortisone is most stable at about pH=4.

5. 2. 3 stability of hydrocortisone in some preparations

Hydrocortisone was unstable in the presence of polyethylene glycols. Polyethylene glycol ointment bases were found to be inappropriate for corticosteroid preparations. This may be due to the presence of peroxides able to catalyse various degradation reactions, or to the presence of minute heavy metal contamination (Allen and Das Gupta 1974; McGinity et al. 1975; Das Gupta 1978).

Hydrocortisone was less stable in preparations containing zinc oxide (Das Gupta 1978). In shake lotions the high alkalinity may be responsible for fast degradation, but an effect of heavy metal impurities or zinc peroxides may play a role too. Finally, adsorption of steroid on zinc oxide particles may be responsible.

Corticosteroids are less stable in preparations containing urea (hydrocortisone, prednisolone). This may be due to the higher pH value of such preparations, but again a specific effect of urea or its impurities cannot be ruled out (Horsch et al. 1984).

These specific instabilities may be expected to be a problem of all corticosteroids. Although the stability of certain steroids may be slightly better than the stability of others, they all exhibit the same kind of degradation pattern and their stability will be comparable.

5. 3 ester hydrolysis

In dermatology corticosteroid esters are generally used. Because they are absorbed better, they are usually more active than the corresponding steroid itself. Hydrolysis of such esters will therefore result in a decreased activity of the preparation. A specific toxicity of the hydrolysis products is not expected.

Apart from total hydrolysis which is usually slow, intramolecular rearrangements may occur. This has for example been extensively documented for betamethasone-17-valerate (Yip and Li Wan Po 1979; Bundgaard and Hansen 1981; Ryatt et al. 1982; Kirsch et al. 1982; Boonsaner et al. 1986). Betamethasone-17-valerate shows a rearrangement to the more stable 21-valerate. The molecular structure favours rearrangement. The 21-valerate may hydrolyse slowly to the corresponding free corticosteroid.

Rearrangement of betamethasone-17-valerate occurs both in the presence and in the absence of water. Ryatt and coworkers found 60% rearrangement in 6 hours in emulsifying ointment (no water present) (Ryatt et al. 1982). Bundgaard and Hansen determined the rearrangement kinetics and found apparent reaction rate constants at 60°C and pH 3.5 of Kobs= 0.21 10^{-2}/h, at pH 7.5 Kobs= 118 10^{-2}/h. The reaction may be acid or base catalysed, or spontaneous (Bundgaard and Hansen 1981). At pH 7.5 and 25°C the estimated shelf life is 1.3 hours. The stability is relatively good in petrolatum and ambiphilic creams (Ray Johnson 1981; Boonsaner et al. 1986). Albert (Albert 1985) also reported a good chemical stability of various unstable drugs in ambiphilic creams.

Betamethasone-17-valerate is about 20 times more active than the 21-valerate, so a dramatic fall in activity will result from the rearrangement reaction. This kind of rearrangement will occur in all 17-monoesters with a free hydroxy group at position 21, but not in 17-monoesters without

such a free hydroxy group like clobetasol propionate, not in 17.21-diesters like betamethasone dipropionate, and not in 21-monoesters like hydrocortisone acetate. As dilution of strong corticosteroids is general practice and accidental dilution with the wrong diluent should be avoided, it may be better to chose a steroid that can be diluted with all generally available dermatological bases, such as clobetasol propionate.

5. 4 acetonides

The stability of corticosteroid acetonides (triamcinolone acetonide, fluocinolone acetonide) as it is reported in the literature is in the same range as that of the corticosteroid itself (Brode 1967, Das Gupta 1983). Rearrangements are not likely to occur and acetonide stability is not expected to be a problem.

5. 5 conclusions

In tropical climates hydrocortisone- and other corticosteroid preparations have a limited shelf life of 1 month at most. Preparations should therefore be prepared immediately before dispensing. Raw materials are fairly stable and may be held in stock for about 2 years if properly packed. The main risk resulting from degraded corticosteroids will be decreased activity. Increased allergic potential may occur, but as glyoxals are unstable their concentration will be low and essentially constant in most corticosteroid preparations. Some steroid esters, specially betamethasone-17-valerate, are unstable and should be avoided.

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6. Stability of phenolic compounds

6. 1 introduction

Phenolic compounds are widely used in dermatological preparations. Phenol for example is used in calamine lotion. In this preparation it is used for several purposes, such as preservation and as an antipruritic. The stability of phenol is limited. The packaging material is important.

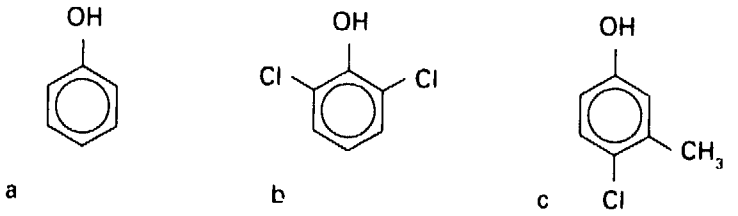

figure 12.6:
molecular formulas of phenol (a), dichlorophenol (b), and chlorocresol (c)

6.2 degradation of phenols

Phenols are degraded by oxidative reactions. The reaction rates are increased by traces of heavy metal ions, light or oxygen. The substituents on the phenol sceleton determine the stability. In general electronegative substituents decrease stability. This explains the decreased stability found by McCarthy for dichlorophenol and chlorocresol (McCarthy 1970). McCarthy found remaining percentages after 3 weeks storage of aqueous solutions in polyethylene bottles of 96.5% for phenol, 78.2% for chlorocresol and only 16.2% for dichlorophenol.

McCarthy found the stability in aqueous solution stored in bottles to be dependent on the packaging materials. After twelve weeks storage of an aqueous solution of phenol in glass 100.9% remained, in rigid PVC 99.8% and in polyethylene 91.1%. This indicates plastic bottles may not be appropriate for the packaging of aqueous solutions of phenolic compounds.

Pure phenol may degrade rapidly if it is exposed to air or light. Degraded phenol is coloured pink to red. Phenol that has a slightly pink colour can still be used, deeply coloured phenol should be discarded.

In airtight containers kept in the dark phenol can be kept for some years. An estimated maximum shelf life for phenol containing preparations is 6 months.

6.3 literature

McCarthy T.J. (1970). Interaction between aqueous preservative solutions and their plastic containers 10. Pharm. Weekbl. 105 1139.

7 Stability of sorbic acid in solutions

7.1 introduction

Sorbic acid is widely used as a preservative in pharmaceutical preparations and in food products. It is unstable.

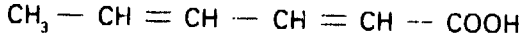

figure 12.7:
molecular formula of sorbic acid

7.2 physical stability

Sorbic acid is volatile at higher temperatures in the presence of water. This effect is seen at temperatures above 75°C. It is not important with solutions stored at ambient conditions. However, if water is boiled during the preparation of creams evaporation of sorbic acid can occur. Boiling of water is necessary to ensure a low contamination of the water, and to ensure the complete dissolution of the sorbic acid. In the preparation of creams preserved with sorbic acid care should be taken to keep evaporation to a minimum.

7.3 degradation reactions

Degradation of sorbic acid occurs via various different free radical, oxidative, reaction mechanisms. Not all mechanisms involved have been fully clarified (Pekkarinen 1972; Arya 1980; Seow and Cheah 1985). Different degradation products are formed, some of which were thought to have antimicrobial activity (McCarthy 1972), but this remains highly speculative (McCarthy et al. 1973).

Heavy metal ions generally increase oxidative degradation, but sorbic acid degradation was decreased by various heavy metal ions (cobalt, copper) (Pekkarinen 1972; Seow and Cheah 1985). This may be caused by the capture of free radicals and termination of radical chain reactions, but this explanation is still purely hypothetic.

pH was a determining factor. Degradation was decreased at higher pH values. This is caused by an electron distribution in dissociated sorbic acid which is less favourable for degradation (Arya 1980). This however is not a feasible stabilisation method as sorbic acid is not active at higher pH.

Oxygen increased degradation. There was a relation between the permeability of the packaging materials for oxygen and the stability of sorbic acid (McCarthy 1970, 1972). Light can also increase degradation.

Antioxidants may be used to stabilise sorbic acid solutions. Stabilisation of aqueous solutions, probably due to antioxidants from packaging materials, has been reported (McCarthy 1970, 1972).

Some emulsifiers, for instance polysorbate 80 may increase degradation (Grusstova et al. 1978).

Water is necessary for the degradation of sorbic acid. When water is absent, sorbic acid is reasonably stable (Seow and Cheah 1985). Highly concentrated solutions have a lower water activity. In such solutions, for example syrups, degradation was slowed down, but this is not a general rule as polyols may also increase degradation (Seow and Cheah 1985).

The package has a great effect on the stability of sorbic acid solutions. Packaging materials may protect sorbic acid directly by limiting the exposure to air and to light. Antioxidants from the packaging material may also have a protective effect especially if they migrate into the solution (McCarthy 1970, 1972).

Degradation finally depends on the concentration, it is less at lower concentrations (Pekkarinen 1972).

7.4 degradation kinetics

Degradation follows (pseudo) first order kinetics (Arya 1980; Seow and Cheah 1985). As in other oxidative degradation processes it is very difficult to calculate the degradation parameters accurately. Stability studies should therefore be done with the final product in the final package. However, some remarks about the stability of sorbic acid can be made.

Arya determined the stability of sorbic acid in aqueous solutions. At 37°C he found an apparent reaction rate constant of Kobs= $0.009.10^{-2}$/h at pH 5 and Kobs=$0.018.10^{-2}$/h at pH 4. Ea was 47 kj/mol (Arya 1980). The shelf lives calculated from these data are 50 days at pH 5 and 25 days at pH 4 (37°C). Iron, copper, manganese and sodium chloride decreased degradation (Arya 1980).

Seow and Cheah determined the degradation at pH 4 in solutions with a lowered water activity of Aw=0.8. At 40°C they found an apparent reaction rate constant of Kobs= $1.45\ 10^{-2}$/d (shelf life 7 days) and an activation energy of 32.6 kj/mol (Seow and Cheah 1985).

These figures differ from each other; perhaps this is due to the presence of sugars in the solution used by Seow and Cheah.

Nielsen found no degradation in a syrup after storage for 26 months (no pH or temperature

stated) (Nielsen 1981). Most bacteria cannot survive in syrups because the osmotic value of the syrup is too high. Some fungi however can survive in syrups and may spoil these. Fortunately, fungi are far more susceptible to sorbic acid than bacteria. So for the preservation of syrups sorbic acid can be used in low concentrations. The low concentration of sorbic acid and the low water activity may have stabilised sorbic acid in the tests of Nielsen.

7.5 conclusions

At the kinetic average temperature in tropical countries sorbic acid is very unstable. This limits its usefulness for tropical dermatological preparations. Sorbic acid containing preparations have shelf lives of one month at best. Because sorbic acid is volatile in the presence of water, special precautions are necessary when creams are prepared.

7.5 literature

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8 Stability of urea

8.1 introduction

Urea is widely used in dermatology, but it is unstable. A good understanding of its degradation reactions is necessary in order to estimate shelf lives for urea containing preparations.

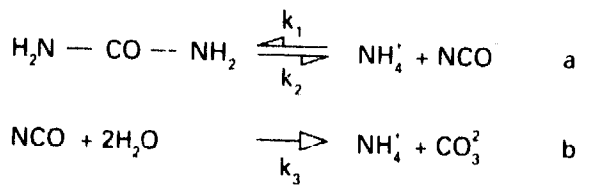

figure 12.8:
degradation of urea

8.2 degradation of urea

Urea degrades via two consecutive hydrolysis reactions (a and b). The first reaction is a reversible reaction, an equilibrium will be formed (Welles et al. 1971; Horsch and Wolf 1985). The equilibrium reaction a) is characterised by the reaction rate constants k1 and k2. Equilibrium kinetics of reaction a) were determined by Welles and coworkers. They found reaction rate constants at 35°C of k1= 1.68 10^{-5}/h and k2= 0.82/mol.h. Activation energies were Ea1=31.6kcal/mol and Ea2=23.6kcal/mol. The equilibrium is characterised by the ratio k2/k1 = [urea]/[cyanate]. At 35°C this ratio is 50.000, and only minute amounts of urea are converted to the cyanate (Welles et al. 1971).

If the temperature is raised the equilibrium shifts to the right because k1 increases faster with increasing temperature than k2. This effect can be calculated. The kinetics were determined in an aqueous solution but the pH was not specified. pH will rise as a result of the establishment of the equilibrium, but this is complicated by evaporation of ammonia (Welles et al. 1971; Horsch and Wolf 1985).

The cyanate formed in reaction a) further degrades to carbonic acid and ammonia in reaction b) (see figure 12.8). This reaction is characterised by the reaction rate constant k3. This implicates the equilibrium a) is not a real equilibrium but an apparent equilibrium, assuming high amounts of urea are present. The reaction kinetics of reaction b) are very complicated because both the reaction products are volatile and they both influence the pH of the reaction medium, generally resulting in a net rise in pH (Horsch and Wolf 1985; Wolf and Horsch 1986a, 1986b).

The overall kinetic parameters of the degradation of urea have not been described. Various authors use various definitions of urea degradation, such as the formation of cyanate, the degradation of urea, the formation of carbonic acid, the formation of cyanate and carbonic acid etc. There are two factors that may complicate the picture further. The first is the impossibility to carry out accelerated stability studies because the relation of temperature and overall reaction rate is too complicated. Too many processes are involved, such as the reactions a) and b), the evaporation of ammonia and carbon dioxide, and dissociation reactions. The second is the fact that degradation is dependent on the initial concentration of urea (Horsch and Wolf 1985; Wolf and Horsch 1986a, 1986b).

Some results of degradation experiments (based on citations in Horsch and Wolf 1985) may be noted here to give an idea of the process:

* Marier and Rose found that in a 20% aqueous solution 0.18% of the urea was converted to cyanate and 0.07% was degraded to ammonia and carbonic acid after storage for 60 days at 25°C.
* Erdey and Kaplar found that after 25 weeks 0.25% of the urea had been degraded (determination of ammonia formed at room temperature, result of reaction a and b).
* Eckert found that after 60 weeks in a 30% solution 0.01% of the urea had been degraded while 0.07% was converted to cyanate (room temperature).
* After 24 hours 2.3% was converted to cyanate and 0.39% degraded, after 80 hours these figures were 2.4% and 1.3% respectively (60°C).

Urea solutions may be stabilised with lactic acid, triacetin or polysaccharides. Of these stabilisers polysaccharides were the most appropriate (Horsch et al. 1984). These stabilisers may influence the therapeutical effectiveness and/or safety. It is therefore better to use urea preparations without stabilisers.

8.3 conclusions

Urea preparations should be freshly prepared and should not be stored for more than one month. When no water is present, urea is relatively stable, it can be kept for more than two years if it is packed in airtight packages (it may absorb moisture from the air).

8.4 literature

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9 Summary of stability data

The following tables summarise the stability data of all materials used in our formulary.

table 12.4:
chemical stability. Abbreviations used are: aq.= aqueous; d=day; m=month; sol.=solution; stab.=stabilised; y=year; <=less than; >=more than; h=hydrolysis; o=oxidation/reduction reactions; teff.=kinetic average temperature; deg. mech.=degradation mechanism. Shelf life is defined as the time in which 10% degradation occurs. For unstable compounds, the degradation mechanism is indicated.

chemical stability material	medium	teff.	shelf life	deg mech.
bentonite		≥ 32.4 °C	> 2y	
benzoic acid		≥ 32.4 °C	> 2y	
benzylbenzoate	raw material	≥ 32.4 °C	> 2y	
	emulsion	≥ 32.4 °C	2y	h
chlorhexidine	aq solution	≥ 32.4 °C	2y	h
	acetate dry	≥ 32.4 °C	> 2y	
dithranol	aq solution	≥ 40.0 °C	< 7d	o
	stab. aq. sol.	≥ 40.0 °C	1 [illegible]	o
	dry	≥ 33.6 °C	[illegible]y	o
gentianviolet		≥ 32.4 °C	> 2y	
glycerine		≥ 32.4 °C	> 2y	
hydrocort.ac.	aq. solution	≥ 40.0 °C	20d (pH=5)	h,o
	dry	≥ 33.6 °C	1y	h,o
iodine		≥ 32.4 °C	> 2y	
lanette wax SX		≥ 32.4 °C	> 2y	
lindane		≥ 32.4 °C	> 2y	
miconazole		≥ 32.4 °C	> 2y	
nystatin	aq. solution	≥ 40.0 °C	< 7d	o
oil (vegetable)		≥ 33.6 °C	1y	o
parabens	aq solution	≥ 32.4 °C	> 2y (pH 3 - 6)	
	dry	≥ 32.4 °C	> 2y	
paraffins		≥ 32.4 °C	> 2y	
phenol	dry	≥ 32.4 °C	2y	o
	aq solution	≥ 33.6 °C	6m	o
potassium permanganate				
	aq solution	≥ 40.0 °C	< 7d	o
	dry	≥ 32.4 °C	> 2y	
salicylic acid		≥ 32.4 °C	> 2y	
silver nitrate	aq. solution	≥ 40.0 °C	< 7d	o
	dry	≥ 32.4 °C	> 2y	
sodium citrate	dry	≥ 32.4 °C	> 2y	
sodium thiosulphate				
	aq. solution	≥ 40.0 °C	< 7d	o
	dry	≥ 32.4 °C	> 2y	
sorbic acid	aq. solution	≥ 40.0 °C	1m	o
	dry	≥ 32.4 °C	2y	o
sulphur		≥ 32.4 °C	> 2y	
tar		≥ 32.4 °C	> 2y	
urea	aq. solution	≥ 40.0 °C	1m	h
	dry	≥ 32.4 °C	> 2y	
zinc oxide		≥ 32.4 °C	> 2y	

table 12.5:
physical stability of raw materials.

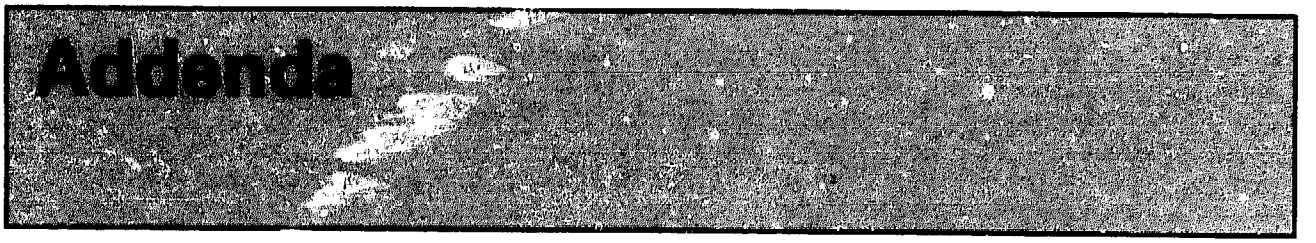
* indicates the problems that may be encountered.

physical stability material	hygroscopic	volatile	melting	crystallization
bentonite	*			
benzoic acid		*		
benzylbenzoate				*
chlorhexidine				
dithranol				
gentianviolet	*			
glycerine	*			*
hydrocort.ac.				
iodine		*		
lanette wax SX			*	
lindane		*		
miconazole				
nystatin	*			
oil (vegetable)				
parabens				
paraffins				
phenol	*	*		
potassium permanganate				
salicylic acid		*		
silver nitrate				
sodium citrate	*			
sodium thiosulphate	*			
sorbic acid		*		
sulphur				
tar		*		
urea	*			
water		*		
zinc oxide				

10 General literature to chapter 12

Fiedler H.P. (1981). Lexicon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete. 2 aufl. Editio Cantor, Aulendorf.

Reynolds J.E.F. (ed) (1982). Martindale, the extra pharmacopoeia 28 ed. The Pharmaceutical press, London.



Addendum A In vitro activity of gentianviolet

Introduction

Gentianviolet and related dyes have been used for decades to treat superficial skin infections. This use was already suggested by Churchman as early as 1912. The dyes are particularly effective against candida species and staphylococci.

In recent years, the dyes are mainly used in tropical countries. There are various reasons for this. Gentianviolet is cheap and readily available, and it is stable. The solution can easily be prepared. There are also therapeutic advantages. Gentianviolet solution has, apart from a definite antimicrobial activity, a drying and astringent effect. This makes it especially useful for the treatment of infections in tropical regions, were profound sweating and wet skin are often important factors in the etiology of skin infections, particularly in candidiasis. Staining of the skin is a main disadvantage, in whites and blacks alike. In industrialised countries other products have taken the place of gentianviolet.

Gentianviolet 1% solution is included in the latest WHO essential drugs list as an anti-infective. However, some doubts have been raised about the suitability of the 1% gentianviolet solution, especially for tropical use. The following three problems are most important:

1. Meurer and Konz found that a 1% solution could cause necrotic skin reactions. They suggested a solution of 0.5% or below should be used.
2. Speck et al found streptococci to be less susceptible to gentianviolet and related dyes in a study on streptococcal colonization of newborns and the relation with umbilical cord care. They even found indirect promotion of streptococcal growth by gentianviolet solution, due to inhibition of staphylococci.
   In temperate zones and under good hygienic circumstances, staphylococci are the main problem. At higher temperatures, higher humidity or poorer hygienic circumstances -this is in fact the situation in tropical third world countries- streptococci are more generally found in primary and secondary pyoderma's. Streptococci are the more dangerous of the two, generally causing deeper infections and in about 1% of all cases complications such as endocarditis and nefritis. Gentianviolet may therefore not be an optimal anti-infective for the tropics.
3. Moats and Maddox found gentianviolet to be less effective at pH values of 6 and below, and brilliantgreen (a related dye) less effective at pH 7 and above. A pH of 6 or below can easily occur on the skin. It may therefore be better to use a combination of both dyes instead of one dye alone.

We were not able to find sufficient quantitative data in the literature on the susceptibility of relevant micro-organisms to gentianviolet and brilliantgreen. We therefore decided to start an in vitro investigation to collect such data.

materials

Micro-organisms were clinical isolates obtained from the department of epidemiology of the university hospital in Groningen (Academisch Ziekenhuis Groningen, the Netherlands). Before each test, micro-organisms were grown overnight on the same medium as used in the test

Gentianviolet was obtained from Aldrich (86, 099-9) and brilliantgreen from Merck (1310). The test solutions were freshly prepared every week. The strongest solution was prepared one day in advance to give the dye time to dissolve. Total dissolution was controlled visually. Three series of test solutions were used, gentianviolet, brilliantgreen and a combination of the two. A

standard concentration range of 0.5 g/100 ml to 0.01 g/100 ml was generally used. The fit of the regression line was checked for the most sensitive organism, *Candida albicans*, with a set of gentianviolet solutions ranging from 10^{-1} to 10^{-6} g/100 ml.

As a growth medium Iso Sensitest Agar (Oxoid CM 471) was used. For the sensitivity tests, 5% defibrinated sheep blood (J. Rottier, Kloosterzande, The Netherlands) was added to this medium. The final pH of this medium is approximately 7.0. For the measurements at different pH values blood was omitted. The pH was adjusted with citric acid for pH 5.4 and with small quantities of hydrochloric acid and sodium hydroxide solution 1N. For dilution and suspension of microbial cultures a buffered peptone/saline solution was used

All measurements were done on 14 cm Petri dishes (Greiner TC-145/20).

methods

measurements

Petri dishes were filled with 60 ml of the sterile medium as a basic layer. This layer was allowed to solidify. An additional 20 ml of the medium was inoculated to contain approximately 10 5 to 10 6 micro-organisms per ml. This was poured over the base layer in the petri dishes to form a top layer. After complete solidification six holes with a diameter of six mm. were punched in the agar layer at regular distances. These holes were filled with the test solutions. The plates were then incubated overnight at 37°C and inhibition zones measured the following morning.

The sensitivity tests were done at least in duple for each solution and for each microbial strain. Three strains were measured of each species, except for group A streptococci (5 strains) and group B streptococci (4 strains). Measurements at different pH values were done in triple on one strain only. One run of measurements consisted of the testing of one microbial strain with all three different sets of dye solutions.

calculations

The logarithm of concentration was plotted against the square of the inhibition zone. A regression line was calculated for each single set of data. The logarithm of the critical concentration was determined by extrapolation of the regression line to zero inhibition. Statistical calculations were done on this logarithm of the critical concentration. Averages were calculated and transformed to concentrations. Standard deviations were calculated on the logarithmic data.

results

table A.1:
Results of susceptability studies; critical concentrations in g/100 ml

	gentianviolet	brilliantgreen	combination
Pseudomonas	$3.6\ 10^{-2}$	>0.5 *	$6.1\ 10^{-2}$
Proteus	$9.2\ 10^{-3}$	$1.4\ 10^{-2}$	$1.2\ 10^{-2}$
Streptococcus A	$2.0\ 10^{-3}$	$9.3\ 10^{-3}$	$5.4\ 10^{-3}$
Streptococcus B	$2.2\ 10^{-3}$	$4.8\ 10^{-3}$	$3.4\ 10^{-3}$
Staphylococcus	$3.8\ 10^{-4}$	$1.7\ 10^{-3}$	$7.5\ 10^{-4}$
Candida	$4.8\ 10^{-5}$	$1.7\ 10^{-3}$	$1.9\ 10^{-4}$

*) not sensitive to the highest concentration used in the test (0.5 g/100 ml).

The measurements at different pH values showed only minor differences between the three types of solutions. However these were statistically significant in some cases. The exact figures are not cited here.

comment

susceptibility

From the data summarized in table a.1 it can be seen that *Candida albicans* and *Staphylococcus aureus* were the most susceptible. Group A and group B streptococci however showed good susceptibility too. The conflicting results of Speck et al in newborns may be due to the fact that they used triple dye solutions once only (triple dye solution contains 229 mg gentianviolet, 229 mg brilliantgreen and 114 mg proflavine hemisulphate per 100 ml of water). Wald et al found group B streptococcal colonization was inhibited by treatment once daily for 5 days with triple dye.

Even the growth of *Pseudomonas* and *Proteus* was inhibited by gentianviolet. The growth of these organisms was inhibited by concentrations even far below 0.5%. These data are consistent with the semiquantitative data of Fung and Miller. We may therefore conclude that a 0.5% gentianviolet solution is active against candida, staphylococci and streptococci.

gentianviolet-brilliantgreen

There was a definite trend in all species to a lower activity of brilliantgreen and the combination solutions at pH 7 on blood agar plates. This was significant in all species except *Proteus* ($p=0.05$). In the pH experiments this trend was also observed at pH 8, while the reverse was seen at pH 5.4 and 6.75. The differences between gentianviolet and brilliantgreen were significant for *Candida albicans* and *Proteus*, but not for staphylococci; the differences between gentianviolet and the combination were significant for *Candida* at pH 5.4 and 6.8 and for *Proteus* ($p=0.05$).

This actually supports the data of Moats and Maddox and Adams. However, differences between the activity of gentianviolet and brilliantgreen were that slight, and the activity of gentianviolet remains that high, that there are no reasons to advocate the use of combination solutions.

vitro-vivo

The data determined here are in vitro data. On the skin -in vivo- other processes may occur, resulting in a lower or higher activity of the dyes. Two important factors however have been ruled out in this experiments. The susceptibility data have been determined in the presence of blood, and hence include a possible inhibition effect of blood. The pH experiments are done on the whole pH range likely to be expected on the skin.

conclusions

From the results of these in-vitro investigations it is clear that gentianviolet is an appropriate anti-infective for the tropics. It is not only appropriate for the treatment of candida infections but it may also be used in the treatment of bacterial infections such as impetigo. The most appropriate concentration is 0.5%, stronger solutions are not necessary but they may provoke necrotic skin reactions.

Addendum B Sedimentation of modified calamine lotion.

Introduction

In calamine lotion sedimentation can occur. Sedimentation should not be too fast. It must be easy to resuspend the sediment. Sedimentation should thus be controlled in pharmaceutical suspensions (see chapter 11.4).

Sedimentation in a suspension may be characterised by the ratio sediment volume/total volume and its change in time. After total sedimentation this ratio characterises the flocculation in the system. The greater the ratio, the more flocculation and the better the resuspendability will be. Resuspendability may be characterised by the number of inversions needed for total resuspension of the sediment.

Materials

Modified calamine lotion was prepared according to the following formula:

zinc oxide	20	g
bentonite	3	g
sodium citrate	0,5	g
glycerin	5	ml
liquified phenol	0,5	ml
waterto	100	ml

All ingredients were pharmaceutical grade.

Methods

The suspensions were stored in 25 millilitre stoppered graduated cylinders at 30°C, 37°C and 45°C. Sediment- and total volume were measured at weekly intervals. The ratio's sediment volume/total volume were calculated. After seven weeks the number of inversions of the cylinders needed for total resuspension was determined.

Results

The results are summarised in table B.1. The number of inversions needed for total resuspension was between 10 and 30, with no differences between the suspensions stored at different temperatures.
The total volume was essentially constant.

table B.1:
ratio sediment volume/total volume.

time	ratio sediment volume/total volume					
	30°C		37°C		45°C	
1 week	0,95	0,96	0,95	0,95	0,94	0,95
2 week	0,91	0,91	0,90	0,91	0,89	0,89
3 week	0,88	0,88	0,87	0,88	0,82	0,82
4 week	0,85	0,84	0,81	0,83	0,81	0,81
5 week	0,82	0,81	0,80	0,81	0,81	0,81
6 week	0,80	0,77	0,79	0,80	0,81	0,81
7 week	0,77	0,74	0,78	0,79	0,81	0,81

Discussion

At higher temperatures the suspension seems to show a tendency to a higher ratio sediment volume/total volume and a more rapid sedimentation. It seems to be more flocculated. This may be caused by a diminished hydration of the particles at higher temperatures. Sedimentation is still very slow. We thus consider the physical stability of modified calamine lotion to be sufficient.

Addendum C Preservation of modified calamine lotion

Introduction

Modified calamine lotion is preserved with phenol (that has, in addition, antipruritic and antiseptic properties). The high pH of the lotion and the presence of large amounts of solid matter (bentonite) prohibits the use of most other preservatives. Three mechanisms may decrease the preservative activity of phenol: dissociation (see chapter 11.4), degradation (see chapter 12.6), and adsorption.

Adsorption to particles may be an important inactivation mechanism for preservatives. Bentonite is an efficient absorbent for preservatives, but more specifically for cationic substances. It was investigated whether adsorption of phenol to bentonite or other constituents of the modified calamine lotion occurs.

Materials

Modified calamine lotion was prepared according to the following formula:

zinc oxide		20	g
bentonite		3	g
sodium citrate		0,5	g
glycerin		5	ml
liquified phenol		0,5	ml
water	to	100	ml

All ingredients were pharmaceutical grade. A "blank" lotion was prepared according to the same formula, but in this case phenol was omitted.

Methods

The lotions were stored at 19°C at constant temperature and humidity. After storage for the time stated the lotions were shaken and samples were taken from the normal and the blank lotion. The samples were centrifuged until the upper layer was only slightly opalescent, this was achieved by centrifugation for 90 minutes at 3500 rounds per minute. The upper layers were then diluted with a 0.1N solution of sodium hydroxide in water and measured spectrophotometrically at 286 nm. The sample of the "normal" lotion was measured against the sample of the "blank" lotion.

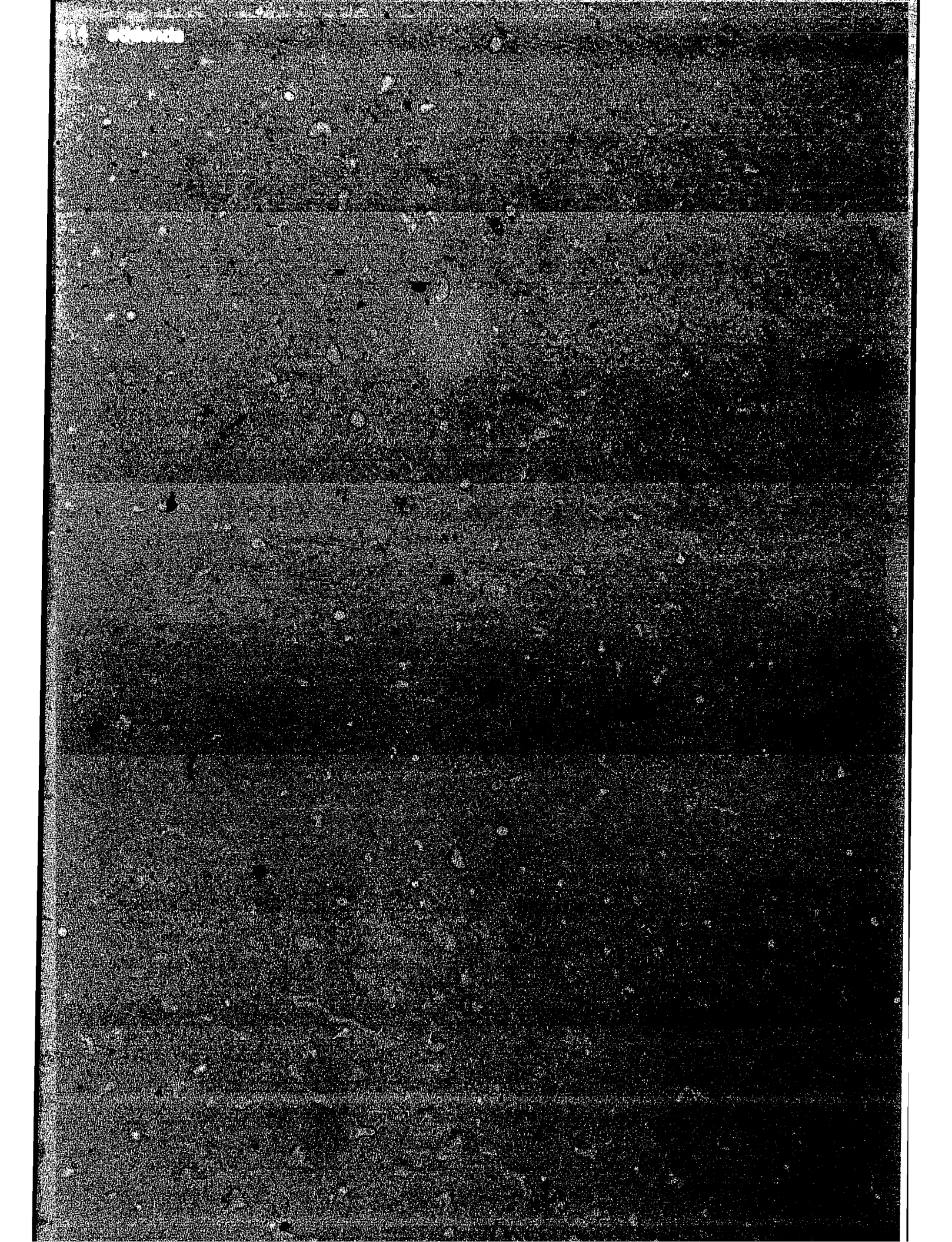
A standard graphic plot of extinction against concentration was used for the calculation of the concentration of phenol in the samples. This standard graphic plot was obtained by measuring extinctions of a solution of the same liquified phenol used for the lotion in a 0.1N solution of sodium hydroxide.

Results

After storage for one day (24 hours) 100.6% phenol was found in the liquid phase of the lotion, after eight days this was 101.0%

Discussion

Adsorption will be less at higher temperatures, it is not a tropical problem. Measurements at higher temperatures are therefore not needed. From the results it can be concluded that practically all the phenol added is present in the liquid phase of the lotion, and adsorption to solid phase constituents of the lotion is practically nonexistent.



13 index

index

Basic cream

batch quantity: 1000 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. lanette wax	150 g				
2. liquid paraffin	125 g				
3. petrolatum	255 g				
4. methylparaben	1,5 g				
5. water	to 1000 g				
6. stock container	1				

Preparation

- Weigh a metal mortar and a plastic pestle. — tare: ..... g
- Melt together lanette was, liquid paraffin and petrolatum in the metal mortar on a water bath and mix.
- Heat this mixture to appr. 70° C. — temperature?:
- Heat 600 ml water to the boil. — water boiled?:
- Dissolve the methylparaben in 500 ml of this boiling water and cool to appr. 70° C. — temperature?:
- Allow the rest of the water to cool.
- Add the water/methylparaben to the fat mixture and mix.
- Stir gently until cold.
- Add enough of the boiled and cooled water to produce 1000 g cream. — weight: tare + 1000 g = ... g
- Pack the cream in the stock container and close well.

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°

shelf life: 2 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials — correct?:
- package — well closed?:
- label — correct expiry date?:

batch released on (date):
by (name):

model of label for stock:

for external use only
basic cream
batch number/date
do not dispense after: (date + 2 months)
if inhomogeneous, mix before dispensing

model of label for the patient:

dispensing unit and date
for external use only
basic cream .....g
name of patient
apply in a thin layer ..... times daily
do not use after: (dispensing date + 1 month)

Benzylbenzoate emulsion 25%

batch quantity: 5 x 200 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. benzylbenzoate	250 g				
2. lanette wax	20 g				
3. water	to 1000 ml				
4. glass bottle of 1000 ml	1				
5. containers of 200 ml	5				

Preparation

- Heat 1000 ml of water to the boil and allow to cool to appr. 70°.
- Melt together the benzylbenzoate and the lanette wax over gentle heat in a metal mortar.
- Add 700 ml of the water of 70° to this mixture and mix.
- Stir gently until cold.
- Calibrate a glass bottle of 1000 ml.
- Poor the emulsion into the glass bottle and add enough water to produce 1000 ml.
- Mix well and distribute over the containers. Close the containers well.

water boiled?:
temperature?:

calibration control:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40° in a dark place

shelf life: 3 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:

for external use only
benzylbenzoate emulsion 25%
batch number/date
do not dispense after: (date + 3 months)

model of label for the patient:

dispensing unit and date
for external use only
benzylbenzoate emulsion 25% 200 ml
name of patient
shake well before use
instructions for use for scabies or lice
(preferably combine with a written leaflet with detailed instructions)

Calamine lotion

batch quantity: 1000 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. zinc oxide	200 g				
2. bentonite	30 g				
3. trisodium citrate (.$2H_2O$)	5 g				
4. glycerine	50 ml				
5. phenol liquified	5 ml				
6. water	to 1000 ml				
7. dark colored glass bottle of 1000 ml	1				

Preparation

- Heat 1000 ml water to the boil and allow to cool. Use this water for the preparation.
- Calibrate the glass bottle for 1000 ml.
- Dissolve the trisodium citrate in 700 ml of water.
- Mix the zinc oxide with the bentonite in a mortar.
- Triturate this zinc oxide/bentonite mixture with the glycerine and 200 ml of the citrate solution.
- Add the rest of the citrate solution and mix until completely homogeneous.
- Add the liquified phenol and mix.
- Put the mixture into the calibrated bottle.
- Rinse the mortar with a little water.
- Add sufficient water to produce 1000 ml of lotion and mix until homogeneous.
- Close the bottle well.

water boiled?:

calibration control:
completely dissolved?:

homogeneous?:

total volume:
homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°
protect from direct sunlight
shelf life: 3 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
calamine lotion
batch number/date
do not dispense after: (date + 3 months)
protect from direct sunlight
shake well before dispensing

model of label for the patient:
dispensing unit and date
for external use only
calamine ..... ml
name of patient
shake well before use
paint the lotion on the skin ..... times daily
and allow to dry; do not cover
do not use after: (dispensing date + 10 days)

Emulsifying ointment

batch quantity: 1000 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. lanette wax	300 g				
2. liquid paraffin	250 g				
3. petrolatum	450 g				
4. stock container	1				

Preparation

- Melt together all ingredients in a metal mortar on a water bath.
- Mix until homogeneous with a plastic pestle.
- Stir gently until cold.
- Pack the ointment in the stock container and close well.

homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 25°

shelf life: 18 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
emulsifying ointment
batch number/date
do not dispense after: (date + 18 months)
if inhomogeneous, mix before dispensing

model of label for the patient:
dispensing unit and date
for external use only
emulsifying ointment .....g
name of patient
apply in a thin layer ..... times daily
do not use after: (dispensing date + 6 months)

Gentianviolet solution 0.5%

batch quantity: 1000 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. gentianviolet	5 g				
2. water	1000 ml				
3. glass bottle of 1000 ml	1				

Preparation

- Heat 1200 ml water to the boil and allow to cool.
- Calibrate the glass bottle for 1000 ml.
- Put the gentianviolet into the glass bottle
- Dissolve the gentianviolet in 1000 ml of water by shaking regularly.
- Check for complete dissolution.
- Close the bottle well.

water boiled?:
calibration control:

no crystals left?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: between 15° and 30°

shelf life: 3 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
gentianviolet solution 0.5%
batch number/date
do not dispense after: (date + 3 months)
check for absence of crystals before dispensing

model of label for the patient:
dispensing unit and date
for external use only
gentianviolet solution 0.5%..... ml
name of patient
apply the solution to the affected part of the skin ..... times daily
do not use after: (dispensing date + 1 week)

Hydrocortisone cream 1%

batch quantity: 100 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. hydrocortisone acetate	1 g				
2. basic cream	99 g				
3. containers for dispensing to the patient as much as needed					

Preparation

- Grind appr. 5-10 g hydrocortisone acetate in a stone mortar.
- Sieve through a 90 µm sieve. — sieved?:
- Weigh 1 g of the sieved hydrocortisone acetate.
- Triturate the hydrocortisone acetate carefully with about 1 g of basic cream until homogeneous in a stone mortar. — homogeneous?:
- Add the rest of the cream in equal amounts and mix until completely homogeneous. — homogeneous?:
- Pack the cream in containers for dispensing to the patient and close well.

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°C

shelf life: 2 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials — correct?:
- package — well closed?:
- label — correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
hydrocortisone cream 1%
batch number/date
do not dispense after: (date + 2 months)
if inhomogeneous, mix before dispensing

model of label for the patient:
dispensing unit and date
for external use only
hydrocortisone cream 1% .....g
name of patient
apply in a thin layer ..... times daily
do not use after: (dispensing date + 2 weeks)

Iodine solution 2%

batch quantity: 100 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. iodine	2 g				
2. potassium iodide	2,5 g				
3. water	to 100 ml				
4. glass bottle of 100 ml	1				

Preparation

- Heat 120 ml of water to the boil and allow to cool.
- Calibrate the glass bottle for 100 ml.
- Weigh the potassium iodide with glass or earthware utensils and put it into the calibrated bottle.
- Add 5 ml of the water and dissolve the potassium iodide.
- Weigh the iodine with glass or earthenware utensils and dissolve it in the solution.
- Add enough water to produce 100 ml and mix well.
- Close the bottle well.

water boiled?
calibration control:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 35° in a dark place

shelf life: 3 months
expiry date:

yield:
loss:
loss due to:

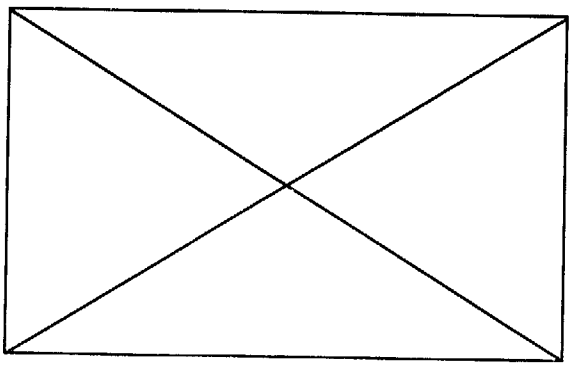
end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
Iodine solution 2%
batch number/date
do not use after: (date + 3 months)



Lindane cream 1%

batch quantity: 20 x 50 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. lindane	10 g				
2. lanette wax	140 g				
3. liquid paraffin	80 g				
4. methylparaben	1,5 g				
5. water	to 1000 g				
6. containers of 50 g	20				

Preparation

- Melt and mix together lanette wax and liquid paraffin in a metal mortar on a water bath to appr. 70°.
- Dissolve the lindane in this mixture.
- Weigh a metal mortar and plastic pestle.
- Heat 750 ml water in the tared metal mortar to the boil and dissolve the methylparaben in this water.
- Allow the water/methylparaben solution to cool to appr. 70 °C.
- Add the lanette wax/paraffin mixture to the water/methylparaben solution under rapid stirring.
- Stir gently until cold.
- Add enough recently boiled and cooled water to produce 1000 g of cream.
- Stir until completely homogeneous.
- Pack the cream in the containers for dispensing to the patient and close well.

temp.?:

tare: ..... g

boiled?:

weight: tare + 1000 g = ...g
homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°
protect from light
shelf life: 3 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
lindane cream 1%
batch number/date
do not dispense after: (date + 3 months)

model of label for the patient:
dispensing unit and date
for external use only
lindane cream 1%, 50 g
name of patient
instructions for use for scabies or lice.
(preferably combine with a written leaflet with detailed instructions)

Potassium permanganate stock solution 1%

batch quantity: 1000 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. potassium permanganate	10 g				
2. water	1000 ml				
3. glass bottle of 1000 ml	1				

Preparation

- Heat 1200 ml of water to the boil and allow to cool.
- Put the potassium permanganate into a glass vessel.
- Add 1000 ml of the water and dissolve the potassium permanganate by stirring.
- Filter the solution over a glass filter.
- Put the solution into the glass bottle and close well.

water boiled?

no crystals left?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: in a cool and dark place

shelf life: 1 month
expiry date:

yield:
loss:
loss due to:

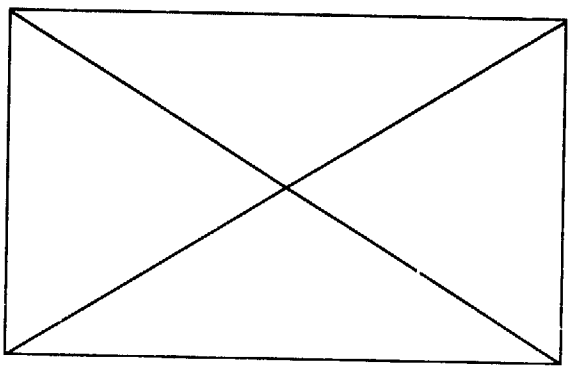
end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
potassium permanganate stock solution 1%
do not use undiluted
batch number/date
do not use after: (date + 1 month)
control for absence of crystals before dispensing



Salicylic acid solution 5%

batch quantity: 10 x 100 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. salicylic acid	50 g				
2. industrial methylated spirit 70%	1000 ml				
3. glass bottles of 100 ml	10				

Preparation

- Put the salicylic acid into a glass vessel.
- Add 1000 ml of industrial methylated spirit 70% and stirr until the salicylic acid is dissolved.
- Put 100 ml in each bottle and close well.

dissolved?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: store in a cool place

shelf life: 2 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
highly flammable
salicylic acid solution 5%
batch number/date
do not dispense after: (date +2 months)

model of label for the patient:
dispensing unit and date
for external use only
highly flammable
salicylic acid solution 5%, 100 ml
name of patient
apply 2 times daily
do not use after: (dispensing date + 1 month)

Silver nitrate solution 0.5%

batch quantity: 1000 ml

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. silver nitrate	5 g				
2. water	1000 ml				
3. glass bottle of 1000 ml	1				

Preparation

- Heat 1200 ml of water to the boil and allow to cool.
- Calibrate the glass bottle for 1000 ml.
- Weigh the silver nitrate with glass or earthware utensils and put it into the calibrated bottle.
- Add 1000 ml of the water and dissolve the silver nitrate.
- Mix well and close the bottle. Do not use a metalic closure.

water boiled?
calibration control:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: in a cool and dark place

shelf life: 1 week
expiry date:

yield:
loss:
loss due to:

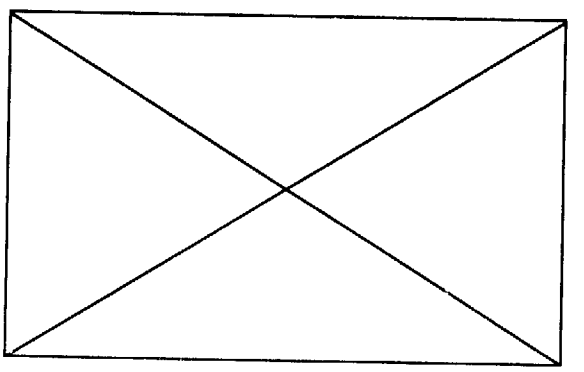
end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
silver nitrate solution 0.5%
batch number/date
do not use after: (date + 1 week)
do not use the solution when it shows a dark discolouration



Sulphur cream 2%

batch quantity: 1000 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. sulphur	20 g				
2. basic cream	980 g				
3. stock container	1				

Preparation

- If the sulphur shows large aggregates, rub it gently between two clean sheets of paper.
- Triturate the sulphur with appr. 20 g of freshly prepared basic cream in a stone mortar with a rough wall.
- Add the rest of the cream gradually and mix until completely homogeneous.
- Pack the cream in the stock container and close well.

homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°

shelf life: 2 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
sulphur cream 2%
batch number/date
do not dispense after: (date + 2 months)
if inhomogeneous, mix before dispensing

model of label for the patient:
dispensing unit and date
for external use only
sulphur cream 2% .....g
name of patient
apply in a thin layer ..... times daily
do not use after: (dispensing date + 1 month)

Tar paste 5%

batch quantity: 1000 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. coal tar	50 g				
2. zinc paste	950 g				
3. stock container	1				

Preparation

- Mix the coal tar with appr. 100 g of zinc paste in a metal mortar. Gentle heat may be used.
- Add the rest of the paste gradually and mix until completely homogeneous.
- Pack the paste in the stock container and close well.

homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°

shelf life: 18 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
tar paste 5%
batch number/date
do not dispense after: (date + 18 months)

model of label for the patient:
dispensing unit and date
for external use only
tar paste 5% .....g
name of patient
apply ..... times daily
to remove rinse with a vegetable oil before washing with water and soap
do not use after: (dispensing date + 6 months)
avoid exposure of treated parts of the body to direct sunlight

Urea cream 10%

batch quantity: 100 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. urea	10 g				
2. water	15 ml				
3. basic cream	75 g				
4. container	1				

Preparation

- Heat 25 ml water to the boil and allow to cool.
- Dissolve the urea in 15 ml of this water.
- Mix the urea solution carefully with an equal amount of freshly prepared basic cream until completely homogeneous.
- Add the remaining amount of basic cream and mix well until completely homogeneous.
- Dispense in a suitable container.

water boiled?:
dissolved?:

homogeneous?:

homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: in a cool place

shelf life: n.a.
expiry date: n.a.

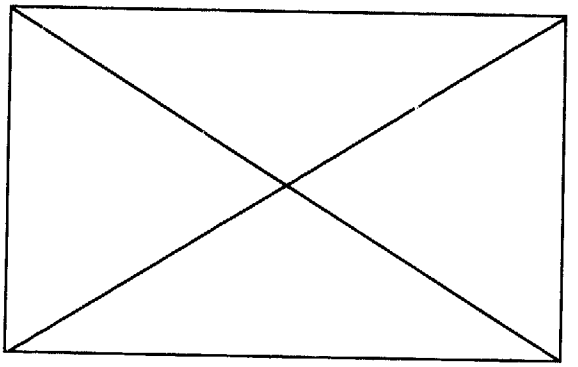
yield:
loss:
loss due to:

end control before release of batch: n.a.

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):



model of label for the patient:
dispensing unit and date
for external use only
urea cream 10% .....g
name of patient
apply in a thin layer ..... times daily
do not use after: (dispensing date + 1 month)

Whitfield's cream 5/5

batch quantity: 1000 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. benzoic acid	50 g				
2. salicylic acid	50 g				
3. basic cream	900 g				
4. stock container	1				

Preparation

- Grind the benzoic acid and the salicylic acid.
- Sieve the powders through a 90 µm sieve, and weigh the amounts needed.
- Mix the benzoic acid with the salicylic acid in a stone mortar with a rough wall.
- Triturate the mixture with appr. 100 g of a freshly prepared basic cream.
- Add the test of the cream gradually and mix until completely homogeneous.
- Pack the cream in the stock container and close well.

sieved?:

homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: below 40°

shelf life: 2 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
Whitfield's cream 5/5
batch number/date
do not dispense after: (date + 2 months)
if inhomogeneous, mix before dispensing

model of label for the patient:
dispensing unit and date
for external use only
Whitfields cream 5/5 .....g
name of patient
apply in a thin layer ..... times daily
do not use after: (dispensing date + 1 month)

Zinc paste

batch quantity: 1000 g

formula approved by:
prepared by:
preparation date:
batch number:

raw materials and packaging materials	quantity	source and batch number	weighed or measured	initials	initials control
1. zinc oxide	500 g				
2. petrolatum	500 g				
3. stock container	1				

Preparation

- Sieve the zinc oxide through a 90 µm sieve and weigh 500 g.
- Melt the petrolatum in a metal mortar over gentle heat.
- Triturate the zinc oxide in a stone mortar with the petrolatum. Mix until no zinc oxide aggregates are left.
- Pack the paste in the stock container and close well.

homogeneous?:

1990 j f m a m j j a s o n d 1991 j f m a m j j a s o n d 1992 j f m a m j j a s o n d

storage: no special requirements

shelf life: 18 months
expiry date:

yield:
loss:
loss due to:

end control before release of batch:

- control of batchnumbers raw materials
- package
- label

correct?:
well closed?:
correct expiry date?:

batch released on (date):
by (name):

model of label for stock:
for external use only
zinc paste
batch number/date
do not dispense after: (date + 18 months)

model of label for the patient:
dispensing unit and date
for external use only
zinc paste .....g
name of patient
apply ..... times daily
to remove rinse with a vegetable oil before washing with water and soap
do not use after: (dispensing date + 6 months)