Chapter Thirty-one

Dentifrices

BASIC REQUIREMENTS OF A DENTIFRICE

The original author of this work laid down the minimum requirements of a dentifrice. Over the years these requirements have changed in emphasis and in content. They are listed below—not necessarily in order of priority:

1. When used properly with an efficient toothbrush it should clean the teeth adequately, that is, remove food debris, plaque and stains.
2. It should leave the mouth with a fresh, clean sensation.
3. Its cost should be such as to encourage regular and frequent use by all.
4. It should be harmless, pleasant and convenient to use.
5. It should be capable of being packed economically and should be stable in storage during its commercial shelf life.
6. It should conform to accepted standards such as British Standards[1] in terms of its abrasivity to enamel and dentine.
7. If prophylactic claims are made, these should be substantiated by properly conducted clinical trials.

Over the past two decades toothpastes have been in a transition stage between cosmetic and prophylactic products. At present the bulk of toothpaste sales is in the prophylactic range, in complete contrast to the situation 25 years ago.

This change has made life more difficult for the formulation chemist who now has the problem, not only of formulating a good cosmetic product, but also of incorporating into it an active ingredient frequently incompatible with normal ingredients.

Over the same period television advertising has grown enormously and the television authorities require that prophylactic and therapeutic claims shall be substantiated. This in turn has meant that dentifrice manufacturers have moved into the area of clinical research in order to produce evidence for their claims. Nevertheless there is still a place for the purely cosmetic product. Indeed, such a product, properly used, probably has some anti-caries effect and should certainly help to prevent gum disorders by improving oral hygiene.

Oral products have appeared in many physical guises, but in convenience terms the most important is the semi-solid paste packed in a collapsible tube. Powders, solid blocks and liquid products can, of course, also be made.

TOOTHPASTES

Basic Structure

The primary function of a dentifrice is to remove adherent soiling matter from a hard surface with minimal damage to that surface. This is a common domestic cleaning situation which is normally solved by using a mildly abrasive powder to which a surface-active agent should be added. The function of the surface-active agent is to aid in the penetration and removal of the adherent film and to suspend removed soiling matter. The foam produced also has a psychological effect in making tooth cleaning more pleasurable.

This cleaning function must be achieved in a short time—say, under two minutes—and at body temperature. The basic formulation would in fact be a simple tooth powder.

The requirement of convenience in packing and in use determines that this basic product should be made into a paste. It thus becomes necessary to add liquids which should have humectant properties to prevent the toothpaste drying out at the tube nozzle. In order to maintain a high-solids suspension in a stable viscous form, it also becomes necessary to increase the viscosity of the liquid phase by the addition of a gelling agent.

Finally it is necessary to add flavours and possibly preservatives, colours and active ingredients, and all these components must be non-toxic and non-irritant under the conditions of use.

The total product should maintain its consistency over a temperature range from 0°C to 37°C (that is, it should have a relatively flat viscosity–temperature curve). It should also be capable of being stored without physical or chemical change over the same temperature range. Most large manufacturers have international sales and may have to take into account local conditions in many countries.

From the manufacturer's point of view the product should be made from the least expensive freely available raw materials compatible with good product quality.

A simple cosmetic toothpaste formulated in this way may have to be modified if an active ingredient is incorporated. In such a case the product virtually becomes a vehicle for the active ingredient and this may affect the basic formulation.

Ingredients

A balanced formula can only be achieved by considering all the ingredients together since many of them may have a dual function or may interact with one another. Cost and availability as well as local laws, regulations and even local habits may cause formulations to vary from country to country.

Abrasives

The abrasive used in a toothpaste must always be a compromise between the ability to clean the surface and the necessity to avoid damage to the tooth surface. In the words of the Council on Dental Therapeutics of the American

Dental Association: 'a dentifrice should be no more abrasive than is necessary to keep the teeth clean—that is, free of accessible plaque, debris and superficial stain. The degree of abrasivity needed to accomplish this purpose may vary from one individual to another'.[2] The abrasivity and cleaning action of abrasives are governed by size, shape, brittleness and hardness.[3,4] The work of Wright[5,6] has led to a clearer understanding of the mechanics of the effect of abrasives on the wear rate of teeth.

The most commonly used abrasives are precipitated calcium carbonate and dicalcium phosphate dihydrate. Other materials include tricalcium phosphate, calcium pyrophosphate, insoluble sodium metaphosphate, various types of alumina, silica and silicates. Particles of plastics may also be used.

Calcium Carbonate. Chalk, or, as it is normally purchased, precipitated calcium carbonate, is available in a number of grades varying in crystalline form, particle size and surface area. Detailed information is available from suppliers and specifications have been established by the Cosmetic, Toiletry and Fragrance Association of America and the Cosmetic, Toiletry and Perfumery Association (formerly the Toilet Preparations Federation) of the United Kingdom.

By varying the conditions of precipitation, precipitated chalks of different densities and crystal habit may be obtained. The two common crystal types are aragonite (orthorhombic) and calcite (rhombohedral) and particle sizes in the range 2–20 μm are normally used.

Chalk is an efficient cleaner but does not produce good lustre on teeth. Grades containing a proportion of particles over 20 μm can also produce scratching on enamel surfaces. Probably the best compromise is to use a small proportion of chalk with a larger proportion of one of the less abrasive phosphates.

Waterworks chalk has been employed in toothpastes but quality is not always uniform and the higher level of water-soluble calcium may cause problems in some formulations.

All chalks give an alkaline reaction to toothpastes and it may be necessary to protect aluminium tubes from corrosion by adding sodium silicate.

Calcium phosphates. The varieties of calcium phosphates used in dentifrices are:

Dicalcium phosphate $CaHPO_4.2H_2O$
Dicalcium phosphate anhydrous $CaHPO_4$
Tricalcium phosphate $Ca_3(PO_4)_2$
Calcium pyrophosphate $Ca_2P_4O_7$

Synthetic apatites have also been proposed as toothpaste abrasives.[7]

Dicalcium phosphate dihydrate (DCP) is the phosphate most commonly used in dentifrices. The pH value of a toothpaste made with DCP is normally in the range 6–8. The taste of DCP-based toothpastes is normally better than that of chalk-based products and the flavour stability is improved.

DCP is in the metastable state and reverts to the anhydrous form with consequent hardening of the paste. This change is accelerated by the presence of fluoride ions. The DCP normally supplied is stabilized to delay or prevent this change. Trimagnesium phosphate, tetrasodium pyrophosphate and calcium sodium pyrophosphate are common stabilizers.[8,9]

Anhydrous DCP is more abrasive than the dihydrate and should only be used in smaller quantities. It is less soluble than the dihydrate and this can be an advantage in fluoride-containing pastes.

Tricalcium phosphate (*TCP*) is not used to a large extent. It too is less soluble than DCP.

Calcium pyrophosphate (*CPP*) was originally developed as the abrasive of choice for products containing sodium or stannous fluoride. The particular form used is patented in many countries. It is claimed that the low availability of soluble calcium ions contributes to the stability of the fluoride.[10,11]

Insoluble sodium metaphosphate (*IMP*) is a particularly useful abrasive for fluoride-containing dentifrices since it contains no calcium ions. It has the minor disadvantage that it contains a small proportion of soluble phosphates.

Other Abrasives. There have been a number of developments in abrasive systems. These have arisen because of particular demands:

(i) the desire to avoid calcium salts in fluoride pastes so as to increase fluoride stability;
(ii) the recent development of transparent dentifrices, that is, dentifrices in which the refractive index of the abrasive is the same as that of the liquid medium in which it is suspended

The first requirement has led to the wider use of hydrated alumina[4] and of synthetic plastics.[12–15] The second requirement led to the use of silica in the form of a hydrated xerogel[16] and sodium aluminium silicates.[17]

Zirconium silicate has also been used in small quantities to impart lustre to the teeth.

Detergents

Tooth cleaning is essentially a detergent process and all toothpastes incorporate a surface-active agent. Soap was the earliest detergent used, but the obvious disadvantages (high pH, taste and incompatibility with other components) has led to its replacement by synthetic detergents.

The detergent must of course be tasteless, non-toxic and non-irritant to the oral mucosa. The foaming qualities are important since they have a significant influence on the subjective assessment of toothpaste performance.

Some surface-active agents may have intrinsic prophylactic or therapeutic properties but in this section they will be considered solely by their detergent function.

Sodium Lauryl Sulphate (*SLS*). Sodium lauryl sulphate is probably the most widely used detergent for oral products and satisfies almost all requirements. In this context 'lauryl' denotes that the alkyl radical R in $ROSO_3Na$ is derived from a narrow cut alcohol predominantly C12 but with some C14. The original sources are palm kernel or coconut oil fatty acids. Various grades are available from manufacturers and particular attention should be paid to taste. This is influenced by the free alcohol content. A low content of inorganic salts is also desirable. Recrystallized grades are excellent in quality but are expensive.

Sodium N-lauroyl Sarcosinate: R.CO.N(Me)CH_2COONa. This compound has been widely used in accordance with a Colgate patent [18] which claims prophylactic effects as a consequence of its anti-enzyme properties. It is particularly useful in oral products because of its high solubility.

Sodium Ricinoleate and Sodium Sulphoricinoleate. Sodium ricinoleate (castor oil soap) has been used in dentifrices where it has the advantage of high solubility, but is vulnerable (as are all soaps) to the presence of calcium ions. Sodium sulphoricinoleate (Turkey Red Oil) has also been used.

Other Detergents. Sodium lauryl ether sulphate ($R(OC_2H_4)_nOSO_3Na$), coco monoglyceride sulphate, alkane sulphonates and alkyl polyether carboxylates have all been proposed as surface-active agents for dentifrices.

Humectants

As mentioned above, it is necessary to incorporate a component with humectant properties to prevent a dentifrice from drying out. This is most likely to happen if the cap is left off the tube. Twenty years ago the only humectant used was a 50 per cent solution of glycerin in water. This is the perfect humectant in the sense that it is stable, non-toxic, has some solubilizing properties and contributes an element of sweetness.

More recently glycerin has been partly or wholly replaced by 70 per cent sorbitol syrup which has similar properties and is usually less expensive. It is available in crystallizing and non-crystallizing grades.

Propylene glycol has also been used as a third component of the humectant system.

Gelling Agents

As mentioned above, it is necessary to incorporate a gelling or binding agent in order to maintain a high-solids suspension in a stable form. The gelling agent also modifies the dispersibility, foam character and 'feel' in the mouth. Gelling agents used in toothpastes are hydrophilic colloids which disperse in aqueous media. These include natural gums such as Irish moss and gum tragacanth, synthetic cellulosic products and silica.

Gum Tragacanth. This gum was extensively used at one time and satisfactory pastes can be made with it. The final product may be variable because of the natural origin of the gum.

Carragheen. This is the generic name given to gums derived from the seaweed *Chondrus crispus* or Irish moss. The purified colloid consists of a mixture of two sulphated polysaccharides and the gelling properties may be controlled by the extent to which the metal ions present—sodium, potassium, calcium and magnesium—have been interchanged by ion exchange.

Commercial carragheens are standardized products of uniform and reproducible quality. Though very commonly used 20 years ago, they have been largely replaced by the cellulose derivatives.

Cellulose Derivatives. These are now the most commonly used gelling agents for toothpastes. Since they are largely man-made they can be tailored to suit any requirement in terms of solubility, gel strength, etc. They are non-coloured, non-toxic and relatively tasteless. Their behaviour in toothpastes has been reviewed by Watson.[19]

Carboxymethyl cellulose (CMC) or, more strictly, sodium carboxymethyl cellulose (SCMC) is prepared by the action of sodium chloracetate on alkali cellulose. The physical properties may be controlled by adjusting the degree of breakdown of the cellulose before substitution and by the degree of substitution.

SCMC gels are anionic and sensitive to pH values outside the range 5·5–9·5. They are reasonably stable in the presence of electrolytes and calcium ions and in general are suitable for most toothpaste formulations. SCMC is indeed the most commonly used gelling agent for toothpastes.

Because it is anionic SCMC is not suitable for toothpastes containing cationic agents such as certain antibacterials. For these a non-ionic cellulose derivative must be used.

One minor disadvantage of SCMC is its possible breakdown if toothpaste is infected with the organism *Penicillium citrinum* but this is a rare occurrence.

Commercial grades of SCMC include Celacol and Courlose (British Celanese), Cellofas and Edifas (ICI), FMP and FHP (Hercules), Tylose (Hoeschst). Official specifications are TPF47 and the CTFA specification (formerly TGA34).

Cellulose ethers are generally the methyl or hydroxyethyl ethers of cellulose. As with SCMC these ethers can be tailor-made to give prescribed properties by varying the degree of substitution. They are of course nonionic and are stable over wide pH ranges and unaffected by metal cations. They are most valuable in formulations that contain antibacterials which are cationic.

Methylcellulose is more soluble in cold than hot water, but since toothpastes can normally be made by cold processes this is no particular disadvantage. Methylcellulose is somewhat incompatible with glycerin and this can be a drawback.

Hydroxyethylcellulose (HEC) has the general characteristics of the cellulose ethers but does not have the inverse solubility/temperature characteristic of methylcellulose. Toothpastes made with HEC are slower to disperse than those made with SCMC so that foam and flavour are slower to develop. Nevertheless HEC is probably nearest to the ideal binding agent for toothpastes, particularly products that contain cations.

Methylcellulose is sold under names such as Celacol (British Celanese), Methocel (Dow), Methofas (ICI), Tylose (Hoechst). Specifications are TPF60 and the CTFA specification (formerly TGA30).

Hydroxyethylcellulose is sold under names such as Cellosize (Union Carbide) and Natrosol (Hercules).

Miscellaneous Gelling Agents. Starch ethers have been used in toothpastes and are satisfactory.

Two synthetic resins, Polyox (an ethylene oxide polymer) and Carbopol (a carboxy-vinyl polymer)—both made by Union Carbide—have also been suggested for use in toothpastes.

A recent newcomer to the field of gelling agents is Laponite (Laporte) which is a synthetic clay of the Hectorite type. This has received some attention in the literature.[20]

Flavours

The flavour of a toothpaste is one of the most important characteristics influencing consumer acceptance. Apart from the matter of consumer reaction the flavour may account for as much as 25 per cent of the unpacked cost of the product. For these reasons it is essential to choose a flavour with great care.

Contrary to popular belief, pleasant-tasting flavours such as fruit, chocolate (even whisky has been suggested!) are not popular. The consumer demands a flavour that is conventionally acceptable (and this varies in different countries) and which leaves a fresh sensation in the mouth and a lasting awareness that the mouth has been cleansed.

Conventionally, flavours have usually been based on the oils of spearmint and peppermint. These are often fortified with a trace of menthol to give a cooling effect. They are also modified with clove (or eugenol) wintergreen (or methyl salicylate), eucalyptus, aniseed, etc.

Wintergreen-type flavours are common in the United States but are less acceptable in Europe, possibly because of the association with embrocations.

All flavours require sweetening and saccharin is the sweetener of choice. Cyclamates are now banned and though a number of other synthetic sweeteners have been proposed none has yet found common acceptance. An important flavour additive has been chloroform which not only has a sweet taste, but promotes a 'flavour burst' sensation in use.

The other components of the toothpaste contribute to the flavour pattern, for example DCP-based pastes have usually a superior flavour to those based on chalk. The flavour may also be modified by the presence of an active ingredient (such as chlorhexidine) and even by the pH of the product.

The nature of the foam and the dispersibility of the paste also affect the flavour impact in the mouth.

These problems can best be solved by creating a flavour panel of expert tasters who can describe and quantify flavour sensations and thus construct a flavour profile.

Other Ingredients

Preservatives. It used to be common practice to add preservatives to the formulation of a toothpaste to protect it from the effect of micro-organisms. The gelling agent for example may be particularly vulnerable. Formalin and sodium benzoate and *p*-hydroxy benzoates were commonly used for the purpose.

The use of preservatives is now less common for a variety of reasons. Formalin is now banned by EEC regulations and sodium benzoate is not effective at neutral and higher pH values. Flavour components themselves have some anti-bacterial action, as have some of the active ingredients now used.

Overriding these considerations, the product should be manufactured in conditions such that the final product is sterile and it should then not be necessary to add preservatives.

Corrosion Inhibitors. Sodium silicate is often added to high pH chalk-based toothpastes to prevent attack on aluminium tubes. Some phosphates also reduce the corrosion risk with alumina-based toothpastes.[21]

Chloroform and high levels of electrolytes can also promote corrosion. Increasing the glycerin level in the water phase will often reduce the risk of this type of corrosion.

Colours. Colours are sometimes added to toothpastes. These must be chosen with care as colour fading, particularly at the nozzle, is not uncommon. The range of colours available is now restricted by EEC regulations.

A novel development was the production of a striped toothpaste by Lever Bros in the USA;[22] this was done by mixing white and red pastes in an ingenious nozzle fitment.

Bleaches. To enhance the whitening effect of toothpastes and powders and to assist in the removal of stains, oxidizing agents are often added to the product. These included sodium perborate, magnesium peroxide, hydrogen peroxide–urea compounds, stabilized hydrogen peroxide compounds, etc. It is doubtful if such compounds remain active after storage and their use has diminished.

Formulation of Toothpastes

The raw materials described above differ not only in constitution but also in their effect on the physical properties of the final product. It is pointless, therefore, to present general formulations except in fairly wide terms. Example 1 gives a general picture of the components of a standard toothpaste.

	(1) *per cent*
Gelling agent	1·0
CMC	
HEC	
Irish moss	
Gum tragacanth	
Humectant	10–30
Glycerin	
Sorbitol 70%	
Propylene glycol	
Abrasive	15–50
$CaCO_3$	
$CaHPO_4 \cdot 2H_2O$	
$CaHPO_4$	
$Al_2O_3 \cdot 3H_2O$	
$Ca_2P_4O_7$	
$MgHPO_4 \cdot 3H_2O$	
SiO_2	
$(NaPO_3)_x$	

(1—*continued*)

	per cent
Sweetener (saccharin)	0·1–0·2
Flavour	1·0–1·5
Spearmint	
Peppermint	
Menthol	
Vanillin	
Eugenol	
Wintergreen	
Anethole	
Anise	
Eucalyptus	
Cinnamon	
Surface-active agent	1·0–2·0
Sodium lauryl sulphate	
Sodium N-lauroyl sarcosinate	
Monoglyceride sulphate	
Preservative (*p*-hydroxy benzoates)	0·1–0·5
Prophylactic agent	0·1–1·0
NaF	
SnF_2	
Na_2FPO_3	
Amine fluorides	
etc.	
Colour (see, for instance, EEC list)	*q.s.*
Water	to 100·0

The addition of fluorides (sodium or stannous) or sodium monofluorophosphate to a toothpaste presents problems so that the above general formula may have to be modified. For example, if free fluoride ions are present in a calcium carbonate formula they will quickly be precipitated as calcium fluoride and the cariostatic activity will be lost. In these cases the abrasive must be chosen with care to prevent or reduce this effect.

Insoluble sodium metaphosphate (IMP) and special grades of calcium pyrophosphate (CPP) are usually used with compounds releasing fluoride ions (for example SnF_2, NaF). Sodium monofluorophosphate is less of a problem since the ion is FPO_3^{2-} and not F^-. In this case DCP and even precipitated calcium carbonate may be used. Great care must be used in all fluoride formulations to ensure that the fluoride activity remains at a high level throughout the life of the product.

The level of fluoride ingredient used has conventionally been such that there is 1000 ppm of fluorine in the final product. This corresponds to 0·2 per cent of NaF, 0·4 per cent of SnF_2 and 0·76 per cent of Na_2FPO_3. In the EEC a proposed amendment to the Cosmetics Directive gives an authorized total concentration of fluoride of 1500 ppm.

Manufacture of Toothpastes

Two basic processes are involved in toothpaste manufacture—the hydration of the gelling agent and the dispersion of the abrasive in the gel. The hydration of

the gel is normally done by adding the solid gelling agent to the glycerin and part of the water under conditions of vigorous agitation. It is not necessary to heat the mixture if CMC is used, but heating to 60°C is usual with Viscarin-type gelling agents. Over-stirring of CMC gels results in an irreversible diminution of viscosity and should be avoided.

Gel hydration can be continuous by means of an eductor (supplied by Hercules) in which the gel powder is introduced gradually into a stream of cold water which is then forced through a nozzle. The vigorous agitation produced gives a smooth uniform gel.

The powder addition may be done in a variety of types of vessel capable of heavy-duty mixing, such as the Petzholdt, Fryma and Unimix vessels. The final mixing is always done under vacuum so as to de-aerate the product. It is usual practice to add the active ingredient (if present) late in the mixing cycle and to add the surface-active agent and the flavour last of all. This is done to avoid excessive foaming and to reduce loss of flavour during evacuation.

The degree to which de-aeration is complete can be checked by density measurement. For a general formula such as that described above, a density of 1·55–1·60 would be expected.

TOOTHPOWDERS

Toothpowders are the original, the simplest and the cheapest compounded forms of dentifrice. Powders have been replaced very largely by the more convenient pastes, but they still hold a small share of the market. Formulation problems are not as severe since interaction between components is unlikely in the absence of water. Fluorides and oxidizing agents, for example, are likely to retain their effective concentration longer than they would do in a paste formulation.

Other formulation problems are likely to be concerned with physical characteristics such as the preparation of ingredients of fairly uniform size so as to prevent separation on shaking, and in ensuring that the product does not cake on storage.

Typical formulations are given in examples 2–5.

	(2)
	per cent
Precipitated calcium carbonate	95·0
Sodium palmitate	5·0
Flavour, sweetener	*q.s.*

	(3)
	per cent
Dicalcium phosphate dihydrate	79·0
Precipitated calcium carbonate	20·0
Sodium lauryl sulphate	1·0
Flavouring, sweetener	*q.s.*

Oxygenated powder	(4)
	per cent
Precipitated calcium carbonate	96·0
Sodium lauryl sulphate	2·0
Magnesium peroxide	2·0
Flavouring, sweetener	*q.s.*

Fluoride powder	(5)
	per cent
Dicalcium phosphate dihydrate	75·0
Precipitated calcium carbonate	23·0
Sodium lauryl sulphate	1·0
Sodium monofluorophosphate	0·8
Flavouring, sweetener	*q.s.*

Manufacture of Toothpowders

The manufacture of powders is very simple. The sweeteners and flavour, together with a little alcohol if desired, are made into a pre-mix concentrate with part of the abrasive powder. This is then mixed with the rest of the powders in a conventional powder mixer.

SOLID DENTIFRICE

Solid dentifrice is essentially a soap in which the abrasive powder is mixed. The proportion of soap may vary within fairly wide limits from about 10 to 30 per cent depending on the glycerin content of the finished product and the hardness desired. It is usual to add a higher proportion of flavour than in paste dentifrices and the product is usually coloured. Solid dentifrices, like tooth powders, have largely been replaced by toothpastes. A typical formula would be:

	(6)
	per cent
Dental soap	18·0
Precipitated calcium carbonate	79·0
Glycerin	3·0
Colour, flavour, sweetener	*q.s.*

The soap and abrasive materials are milled with the glycerin and sufficient water to give a plastic mass. Colour and flavour are added and the product is then plodded and extruded in a conventional soap plodder, cut into billets and stamped.

The abrasive nature of the product demands specially fabricated plodders and cutters, and in general the manufacture of solid dentifrices presents a number of problems.

PERFORMANCE TESTS

The clinical claims made for dentifrices and the restraints on advertising have helped to increase the volume of work done in recent years on the performance

of dentifrices. Biological material in the form of extracted human and animal teeth is readily available and some experimental work can even be done on teeth *in situ* in the mouth. Chemists, physicists and dentists have all contributed to the vastly increased knowledge of the performance of oral products.

Abrasive Action

The cleaning properties of a dentifrice depend primarily on the nature and quantity of abrasive present; the design of the toothbrush may play a part and even the detergent, but their effects are insignificant compared with that of the abrasive.

During cleaning, food debris, plaque, acquired pellicle, stains and calculus should be removed from the tooth surface, if possible without damage to the underlying enamel. Dentifrice abrasives are a compromise between the desire for perfect cleaning and the desire to avoid enamel wear; evaluation methods and the standards adopted reflect this compromise.

There is now no doubt in the minds of experts in this field that abrasion studies must be done on human dentine and enamel and not on other substrates. The use of a metal substrate can often produce misleading results. The most obvious method of measuring abrasion should be by weight loss, but this requires excessive abrasion and would lead to wear far in excess of that met with in a real life situation.

A variety of techniques has been proposed for the measurement of the abrasive quality of toothpastes, for example the shadowgraph method,[23] the surface profile method,[24] interference microscopy[25] and replication techniques.[26] There is now almost universal agreement that the technique most nearly approximating to natural conditions is the radio-tracer method first described by Grabenstetter *et al.*,[27] further developed by Wright[5,6] and finally incorporated in a British Standard.[1]

Specimens of tooth crown (enamel) and root (dentine) are bombarded with neutrons which change a minute fraction of the phosphorus atoms present from ^{31}P to ^{32}P. After brushing under standard conditions the slurry of toothpaste used is dried and counted for β emission. By comparison with a standard toothpaste of fixed composition it is possible to give a relative abrasivity rating to any toothpaste. The British Standard sets the figure of 100 as the abrasivity rating of the standard (a conventional chalk dentifrice) and sets the maximum allowable abrasivity of a toothpaste as 200 against dentine and 400 against enamel. This reflects the greater vulnerability of the much softer dentine.

In fact almost all conventional toothpastes fall comfortably within this standard; abrasivity ratings of 50–100 against dentine and 50–120 against enamel would probably cover most commercial toothpastes.

There is no evidence to show that any conventional dentifrice, *when properly used*, has caused excessive wear of enamel or dentine. Cervical erosion, that is, erosion at the neck of tooth following gum recession, which occurs in older subjects, is due to bad brushing technique.

The amount of material lost by abrasion with a relatively abrasive paste has been calculated as $1{\cdot}2 \times 10^{-8}$ g per brush stroke from enamel and 98×10^{-8} g per brush stroke from dentine.

Using the radio-tracer technique it is possible to assess the relative wear rates of different particle sizes of different abrasives. Within the fairly narrow limits of conventional toothpaste formulations there is an almost linear relationship between (a) particle size and wear rate and (b) percentage concentration of abrasive and wear rate.

Hardness, crystallinity of particles and particle shape all play some part in determining wear rate, but with the knowledge and experience available to the expert it is now possible to pre-set the abrasivity of a toothpaste within fairly narrow limits. Probably the best compromise would be to have a relatively high proportion of large soft particles (e.g. DCP 5–10 μm in size) and a small proportion of small hard particles (e.g. zirconium silicate or silica 1 μm in size). The large soft particles should remove most of the adherent soiling matter from teeth and the small particles should give some degree of polish without visible scratching.

Lustre (Gloss or Polish)

The measurement of lustre is complicated by a number of factors. Hunter[28] has pointed out that it is impossible to measure specular reflectance and diffuse reflectance as separate entities in any but an approximate way, and describes six different kinds of gloss:

1. *Specular gloss*—shininess.
2. *Sheen*—surface shininess at grazing angles.
3. *Contrast gloss*—contrast between specular reflectance of different areas.
4. *Absence-of-bloom gloss*—the absence of reflection haze or smear adjacent to highlights.
5. *Distinctness-of-reflected-image gloss*—distinctness of images reflected in surfaces.
6. *Absence-of-surface-texture gloss*—lack of surface texture and surface blemishes.

This is a highly sophisticated analysis of the problem of lustre determination and is probably too complex for measurement on human teeth. The simplest assessment of lustre on teeth is a subjective one and what is required is a simple objective procedure which will duplicate subjective assessment.

In the paint and lacquer industry a test method has been described[29] the basic principle of which is the illumination of the test specimen with a parallel beam of light and the measurement of the reflection of this beam at a predetermined angle. It appeared to Tainter[30] and co-workers that this method could be modified for the measurement of directional reflectance. Considerable refinement of apparatus and technique was necessary to adapt this method to measurements of gloss on teeth because of their small size and the curvature of the enamel surface. As a result of their experiments Tainter *et al.* published their quantitative method for measuring the polish produced by dentifrices.[31]

Phillips and Van Huysen[32] reported the results of an investigation into the action of dentifrice polishing agents on the tooth surface. Two methods were employed: (i) visual observation of lustre changes by comparison with a series of

standards and (ii) microscopic study of the tooth before and after brushing. As a result of their work it was concluded that calcium carbonate tended to dull enamel surfaces. Calcium phosphates (DCP and TCP) had little effect on lustre, while a mixture of metaphosphate and calcium phosphate appeared to be superior to other abrasives. It would be unwise to be too dogmatic on this subject since the degree of lustre on the one hand and dulling on the other are strongly influenced by mean particle size and the range of particle size of the abrasive concerned.

The depth of scratches measured by profilometer techniques has been found to correlate with polishing power and this again emphasizes the importance of particle size. Manly *et al.*[33] used a similar technique in measuring the scatter of a laser beam and Schiff and Shaver[34] have adapted Tainter's methods to measurement of polish *in vivo*. Probably the simplest assessment of polish and cleaning power is the technique described by Wilkinson and Pugh[4] who showed that there is a direct relationship between abrasion and cleaning power. It should thus be possible to devise an abrasive system to give both adequate cleaning and minimum abrasion. A mixture of large (10 μm) soft crystals with a minor proportion of small (1 μm) hard crystals should achieve this result.

THE TOOTHBRUSH AND TOOTHBRUSHING

The toothbrush and the mechanism of toothbrushing play an important part in oral hygiene.

Surveys of toothbrushing habits[35,36] show that 60 per cent of adults claim to brush their teeth twice a day, usually on waking and before going to bed, and that on the whole women are more conscientious than men. This is a very superficial picture, however; the statistics of toothpaste sales in different countries show clearly that a large number of people either do not brush their teeth at all, or do it rarely.

It has never been shown unequivocally that toothbrushing alone is instrumental in reducing dental decay. Fosdick[37] has shown that regular brushing with a cosmetic dentifrice reduces the incidence of decay among susceptible subjects, while Smith and Striffler[38] in a review of the literature found some evidence to the contrary. What is surely beyond question is that the frequent use of a fluoride dentrifrice does reduce the incidence of decay. This has been demonstrated in a large number of clinical trials.

It is also clear that regular toothbrushing is effective in reducing or preventing periodontal disease. The removal of food debris and the massaging of the gums are a part of good oral hygiene.

A case can therefore be made for regular toothbrushing with a good prophylactic toothpaste:

(i) It is aesthetically satisfying to produce a clean fresh sensation in the mouth.
(ii) A good prophylactic toothpaste will certainly reduce the incidence of caries.
(iii) The removal of food debris should improve mouth odour.
(iv) Regular brushing will help to prevent periodontal disease.

The introduction of the electric toothbrush has stimulated tests designed to show whether mechanical brushing is superior to hand-brushing. Unfortunately, there are no accepted criteria for evaluating the effectiveness of a toothbrush. Prevention or removal of plaque and calculus, the gingival index and the absence of staining are all common criteria. The evaluation is further complicated in that toothbrushes vary not only in head size and basic design, but also in the bristle pattern and the nature and stiffness of the bristle. In a review of this subject, Ash[39] concluded that electric toothbrushes were no more effective than manual toothbrushes for the average subject, but that individuals might find one or other to be more effective.

McKendrick *et al.*[40] performed a two-year study on dental students comparing manual and electric toothbrushes and found a lower periodontal index in all subjects but no significant difference between groups.

Muhler[41] found that the frequency of use of electric toothbrushes rose from 1·04 to 2·90 times per day after two months and declined thereafter. After one year half the subjects gave up this method of cleaning teeth. During the same period, the subjects using manual brushes did not alter their frequency of brushing.

Other devices have been suggested for cleaning teeth. An elongated brush with a flexible abrasive string attached has been proposed,[42] as have water jet rinsing devices[43] and water jets containing abrasives.[44] These methods have been reviewed[45,46] and it has been found that though they may be effective in reducing the population of micro-organisms on the tooth, they are not as effective as toothbrushes for the removal of oral debris.

It can be assumed that most brushes, properly used, have some effect in improving oral hygiene and hence periodontal disease, but no case can be made for their having any anti-caries effect. In general, professional dental care, proper diet, the use of a prophylactic dentifrice and education in brushing technique are essential features in the prevention of oral diseases.

DENTURE CLEANSERS

Denture cleansers are marketed either in powder or tablet form or as liquids. Though the solid products may differ widely in composition, they comprise essentially an oxidizing agent, an electrolyte and an alkali.

The oxidizing agent used is normally sodium perborate or sodium percarbonate, though hypochlorites, trichlorisocyanuric acid and its salts and persulphates have also been used or proposed.

Sodium percarbonate is more soluble in water than sodium perborate, but is not quite so stable, though in the solid form its stability is adequate.

Sodium perborate is available in two forms:

(i) *Sodium perborate tetrahydrate*, usually written as $NaBO_3 \cdot 4H_2O$ but more properly $NaBO_2 \cdot H_2O_2 \cdot 3H_2O$, has an active oxygen content of 10·38 per cent and is sold on the basis of 10 per cent active oxygen.

(ii) *Sodium perborate monohydrate*, usually written as $NaBO_3 \cdot H_2O$ but more properly $NaBO_2 \cdot H_2O_2$, has an active oxygen content of 16 per cent and is sold on a basis of 15 per cent active oxygen.[47]

Sodium percarbonate, like sodium perborate, is not a true persalt and should be written as $2Na_2CO_3 \cdot 3H_2O_2$.

The purpose of a denture cleanser is to loosen debris, which consists of saliva and food particles, to remove stains and to sterilize the denture.

Solid products are normally dissolved in water to form a solution in which the denture is immersed. Bubbles of oxygen form and help mechanically to loosen food debris which is itself partly solubilized by the alkali present. Electrolytes such as sodium chloride have some solubilizing action on mucous deposits. The combined effect is to loosen the debris so that, after a suitable period of soaking, it is easily brushed away.

In addition the denture is sterilized and stains are removed. Regular use of denture cleansers will also prevent the build-up of calculus on the denture surface.

Whatever the form of oxidizing agent used, care must be taken to ensure that the product does not alter the colour of the dental plate, though this danger is much less now than formerly. Modern plastic dental plates normally retain their colour well.

The amount of sodium perborate or percarbonate used is usually in the range 20–50 per cent; corresponding amounts of other oxidizing agents may be employed with the proviso that active chlorine-producing compounds should be used at such a level as to leave the denture, after rinsing, without an unpleasant chlorine after-taste.

The electrolyte used is invariably sodium chloride and the alkali is most commonly anhydrous trisodium phosphate, though sodium carbonate or bicarbonate and other alkalis may be used.

Typical formulae are given in examples 7 and 8.

	(7) *per cent*
Sodium perborate	40·0
Sodium chloride	30·0
Trisodium phosphate	30·0
Flavour, colour	*q.s.*

	(8) *per cent*
Sodium percarbonate	40·0
Sodium chloride	40·0
Sodium carbonate	20·0

Tablets can also be prepared, either from conventional mixtures as in examples 7 and 8, or as, for instance, in example 9.

	(9) *per cent*
Sodium percarbonate	88·0
Sodium chloride	10·0
Sodium silicate and/or other binders	2·0
Flavour, colour	*q.s.*

Liquid products are normally dilute solutions of sodium hypochlorite to which additional sodium chloride may be added. Such solutions of course lose some of their available chlorine over time.

It is common to promote effervescence in some solid products. This helps in the break-up and dissolution of tablets and promotes the concept of activity. Effervescence may be provided by the addition of conventional carbonate–acid mixtures (tartaric or citric acids) or by the incorporation of a peroxide-decomposing catalyst such as a trace of a copper salt. In the latter case great care should be exercised in checking the stability of the finished product.

The inclusion of proteolytic and amylolytic enzymes in denture cleansers[48] has been proposed. Other new developments are most easily found in patent literature.[49]

The manufacture of these products is not as simple as it appears. It is vital to keep moisture out of the product and to protect it from atmospheric humidity. The powder products must not cake on storage and solid products should dissolve quickly to give a clear solution.

Stringent age testing should be performed on the packed product and the continued performance of the product under usage conditions should be monitored.

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Chapter Thirty-two

Mouthwashes

Introduction

In principle a mouthwash appears to be the ideal means for the application of any form of medication to the mouth, the gums or the teeth—provided, of course, that the tooth surface has been cleaned.

McCormick[1] has reviewed the literature on mouthwashes. In general they may be any of three types: antibacterial, which deal with the bacterial population of the mouth; fluoride, which help to reinforce the fluoride layer of the enamel of teeth; and remineralizing, which help to repair early carious lesions. This chapter deals only with mouthwashes of the antibacterial type. Such products are expected by the consumer to give a healthier and fresher mouth and to provide some assurance of good breath odour. Specific studies on the caries-preventive properties of mouthwashes containing fluoride have been described by Birkeland and Torell.[2]

Antiseptic mouthwashes have not attained a high level of sales in the UK, but they are popular in other countries, particularly in the USA where sales value in 1978 amounted to $269 million.[3] In general, the American mouthwashes have been formulated to be ready for use, while European mouthwashes have tended to be used after dilution.

Mouthwashes have normally been marketed on the basis of a social necessity for clean breath, though recent work with chlorhexidine has shown that they may have anti-plaque properties[4] and indeed even anti-caries properties.[5]

It is of course neither possible nor desirable to aim at complete sterility in the mouth. The use of antibiotics, for example, might destroy normal bacteria and thus permit the growth of undesirable organisms such as *Candida albicans*. It is possible, however, to reduce the bacterial population and maintain it at a lower level by the use of antibacterials which are adsorbed onto the mucous membrane. Cationic antibacterials normally have this property to some degree. The Buccal Ephithelial test of Vinson and Bennet can serve as a standard technique.[6]

The total effect exerted is a combination of three factors: (a) the mechanical effect of rinsing food debris from the mouth; (b) the effect of the antibacterial agent on the oral flora; and (c) the effect of the flavour present. Since many flavouring substances have an antibacterial effect, there may be synergism between (b) and (c).

Mouthwashes which merely claim to promote general oral hygiene should nevertheless be rigorously tested for absence of toxic and irritant properties. Prophylactic and therapeutic claims would require even more stringent clinical tests and should be regarded in the light of the regulations of the Federal Drug Administration of the USA and the Medicines Act (1968) in the United Kingdom. There are also EEC regulations covering individual ingredients.

Stock formulations are available from recognized sources such as the Pharmaceutical Formulary (Chemist and Druggist), Extra Pharmacopoeia (Martindale), etc. Products discussed below are examples that are known to be acceptable to consumers.

Choice of Antibacterial Agent

The antibacterial agents usually employed in mouthwashes include phenols, thymol, salol, tannic acid, chlorinated thymols, hexachlorophene and quaternary ammonium compounds.

Chlorinated Phenols

*Para*chlormetacresol and *para*chlormetaxylenol are both suitable for use in mouthwashes, both for their antibacterial properties and their flavour. They are not very soluble in water but may be solubilized with terpineol (or other suitable solubilizer) and soap to give a 1 per cent solution of active material. Such solutions, for example Liq. Chloroxylenol BPC, are used at 10–20 per cent dilution.

Soap-based Mouthwashes

Soap-based mouthwashes normally have no antibacterial properties and are used to clean and freshen the mouth.

	(1) *per cent*
Powdered soap	2·0
Glycerin	15·0
Alcohol	20·0
Water	63·0
Flavour	*q.s.*

Synthetic detergents which are non-irritant may be added to give extra foaming and of course standard antibacterials may also be added to this basie formula.

Thymol (Isopropyl Metacresol)

Thymol is not very soluble, but may be solubilized in the normal way, for example with suitable alcohols, or used in aqueous solution with borax as in example 2. This product is used diluted to between 5 and 20 per cent concentration.

	(2) *per cent*
Thymol	0·03
Alcohol	3·00
Borax	2·00
Sodium bicarbonate	1·00
Glycerin	10·00
Flavour	*q.s.*
Water	to 100·00

Hydrogen Peroxide
Hydrogen peroxide is an excellent non-toxic antibacterial agent for use in mouthwashes. It can be used for cleansing ulcers and abscesses in the mouth, etc. A solution of one part hydrogen peroxide (10 vol.) diluted with 8 parts of water is useful as a mouthwash, or twice the strength can be used for septic cavities. Because of its instability it is not normally used in proprietary mouthwashes.

Sodium perborate, however, is a stable powder which on dissolving in water gives an alkaline solution of hydrogen peroxide. In practice 17 g of such a powder with 6 g of citric acid will, on the addition of 80 ml water, give a solution of 10 vol. strength which should be further diluted 1:8 before use.

Such products should be used only sparingly and to combat specific conditions, since the citrate present could lead to decalcification of the teeth.

Hexachlorophene
Hexachlorophene is substantive to the mucous membrane and is an effective antibacterial agent. The suggested concentration is 0·02 per cent in a 25 per cent alcohol–water mix. Some reservations have been expressed with regard to possible toxicity.

Quaternaries
The use of quaternaries is now well established in mouthwashes. These compounds combine antibacterial and substantive properties and many of them are non-toxic and non-irritant at the concentrations normally used. Because of their antibacterial properties many of them are effective against plaque. Benzethonium chloride is used for this purpose, but probably the most effective antibacterials are of the chlorhexidine type. Unfortunately chlorhexidine, in common with most cationics, can produce a brown stain on teeth with continued use. However, this stain is easily removed with good toothbrushing.

A product of this type has been presented in the form of a gel, which, though intended for brushing onto the teeth, is really a mouthwash rather than a toothpaste since it contains no abrasive.[7]

Other Mouthwash Components
Tannic acid, alum and zinc salts have all been used in mouthwashes because of their astringent properties. It is generally assumed that because of this property they have anti-bleeding effects on the gums.

A dilute solution of sodium hypochlorite is also commonly used because of its antibacterial effect. Formalin was formerly used, but is now prohibited under EEC regulations.

Flavouring of Mouthwashes

An essential feature of a good mouthwash is its flavour, since the consumer must be aware of the freshness of the mouth after use. Money spent on market research is well invested since there are national preferences for particular flavours; for example, methyl salicylate (oil of wintergreen) is more popular in the USA than in the United Kingdom.

Peppermint, menthol, eugenol, etc. are commonly used flavours and all leave the mouth with a feeling of freshness. Chlorinated phenols always have a characteristic flavour which, though not unpleasant, is difficult to cover. Cationics normally are slightly bitter and must be covered. The small manufacturer would be well advised to use the services of a flavour house to design a compounded flavour unique to his product.

Aerosol Mouth Fresheners

Aerosol mouth fresheners, a natural development of aerosol products, are marketed in the USA and in Europe. They are recommended for freshening the breath after eating, drinking or smoking and usually contain only flavouring agents, though antibacterials could be added. Aerosol mouth fresheners are thus presented rather as an alternative to chewing gum than as mouthwashes.

A typical $\frac{1}{2}$ oz (14 g) pack is fitted with a metered valve and contains sufficient product for 200–300 applications. A metered valve is not essential, but does protect the consumer from excessive amounts of product entering the mouth.

One significant advantage of this form of presentation is that the container is small enough to be carried in the handbag or pocket, so that its use is not confined to the bathroom.

Some manufacturers market breath freshener dispensed as a liquid. One drop placed on the tip of the tongue is claimed to produce instant freshness and the removal of breath odour.[8]

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PART FIVE

Product Ingredients and Manufacture

Chapter Thirty-three

Surface-active Agents

Introduction

The fundamental phenomenon of surface activity is *adsorption* which can lead to two quite distinct effects: (a) lowering of one or more of the boundary tensions at interfaces in the system, and/or (b) stabilization of one or more of the interfaces by the formation of adsorbed layers.[1]

A surface-active agent (surfactant) is a material which, by use of this phenomenon, has the property of altering the surface energy of a surface with which it comes into contact.[2] This lowering of surface energy can easily be observed in, for example, foaming, the enhanced spreading of a liquid on a solid, the enhanced suspension of solid particles in a liquid medium and the formation of emulsions.

The use of surfactants is well established in cosmetics and toilet products and falls into five main areas depending on the surface-active properties required:

1. *Detergent*. Where the main problem involves the removal of soiling matter, surface-active agents with detergent properties are needed, for example in shampoos and toilet soaps.
2. *Wetting*. In products where good contact is required between a solution and a substrate, good wetting properties are required, for example in the application of hair colorants and permanent waving lotions.
3. *Foaming*. Some products need to have a high level of foam in use, and for these products special surface-active agents are used, for example in shampoos and foam baths.
4. *Emulsification*. In products where the formation and stability of an emulsion is a vital feature, surface-active agents with good emulsifying properties are required, for example in skin and hair creams.
5. *Solubilization*. Products in which it is necessary to solubilize an insoluble component need a surface-active agent with the appropriate properties, for example the solubilization of perfumes and flavours.

These qualities are not mutually exclusive; they are shared to some degree by all surface-active agents. Experience has shown the value of particular products for various end uses, but there is a large degree of overlap.

Classification of Surfactants

All surface-active agents have one structural feature in common: they are all amphipathic molecules; that is, the molecule has two distinct parts—a hydrophobic unit and a hydrophilic unit.

Hydrophobic units are usually hydrocarbon chains or rings or a mixture of the two. Hydrophilic units are usually polar groups such as carboxylic, sulphate or sulphonate groups, or, in nonionic surfactants, a number of hydroxyl or ether groups. The dual nature of these molecules allows them to adsorb at interfaces and this accounts for their characteristic behaviour.

Surfactants may be classified on the basic of the uses to which they may be put, on the basis of their physical properties or on the basis of chemical structure. None of these is entirely satisfactory, but probably the most logical is to classify them according to their ionic behaviour in aqueous solution. Using this procedure there are four types of surfactant—anionic, cationic, nonionic and ampholytic surfactants. In addition, the different structures of the hydrophobic and hydrophilic groups have to be considered. Schwartz and Perry,[2] McCutcheon,[3,4] and Moillet, Collie and Black[1] have all used this classification system.

Anionic Surfactants

Anionic surfactants are those molecules in which the surface-active ion is negatively charged in solution. The classic example is soap: $C_{17}H_{33}COO^-Na^+$ (sodium oleate). The anionic surfactants are further subdivided according to the manner in which the anionic group is attached to the hydrophobic part of the molecule (Table 33.1).

Cationic Surfactants

Cationic surfactants are characterized by the fact that the surface-active ion is positively charged in aqueous solution (Table 33.2).

Nonionic Surfactants

Nonionic surfactants are characterized by the fact that the hydrophilic part of the molecule is usually made up from a multiplicity of small uncharged polar groups, for example hydroxyl groups or the ether linkages in ethylene oxide chains. The same linkages are used to reinforce the hydrophilic character in certain anionic surfactants, for example alkyl ether sulphates, $R(OCH_2CH_2)_nOSO_3^-\ M^+$ (Table 33.3).

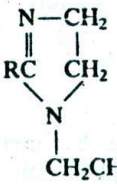
Ampholytic Surfactants

Ampholytic surfactants are characterized by their ability to form a surface-active ion with both positive and negative charges (Table 33.4).

Properties of Surface-active Agents

The change in surface properties as the concentration of an aqueous solution of a surfactant rises is characteristic of most surface-active molecules. For example, as concentration rises the surface tension of an aqueous solution of, say, sodium dodecyl sulphate ($C_{12}H_{25}OSO_3Na$) falls rapidly (Figure 33.1), with corresponding changes in the physical properties such as interfacial tension, electrical conductivity, etc. At a certain concentration level a discontinuity occurs and surface tension and other properties no longer fall. The concentration at which this discontinuity occurs is called the *critical micelle concentration* (CMC).

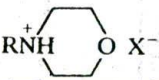
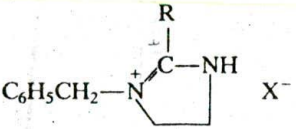
Table 33.1 Anionic Surfactants
R denotes a hydrophobic chain usually of 12 to 18 carbon atoms, or a ring or system of rings.
M represents a suitable cation, usually sodium, potassium, ammonium or an organic base.

Anionic groups connected directly to the hydrophobic unit	
Fatty acid soaps	$RCOO^- M^+$
Alkyl sulphates	$ROSO_3^- M^+$
Alkyl sulphonates	$RSO_3^- M^+$
Alkyl aryl sulphonates	$RC_6H_4SO_3^- M^+$
α-Sulphonyl fatty acids	$RCH(SO_3^-)COO^- M^+$
Secondary alkyl sulphates	$RCH(OSO_3^-)R' M^+$
Alkyl phosphates	$ROPO_3^{2-} 2M^+$
Anionic groups connected through ester links	
Monoglyceride sulphates	$RCOOCH_2CHOHCH_2OSO_3^- M^+$
Dialkyl sulphosuccinates	$ROCOCH_2CH(SO_3^-)COOR M^+$
(R usually C_8—C_{10})	
Polyethyleneglycol ester sulphates	$RCO(OCH_2CH_2)_nOSO_3^- M^+$
Isethionates	$RCOOCH_2CH_2SO_3^- M^+$
Anionic groups connected through ether links	
Alkyl ether sulphates	$R(OCH_2CH_2)_nOSO_3^- M^+$
Phenol ether sulphates	$RC_6H_4(OCH_2CH_2)_nOSO_3^- M^+$
Alkyl ether carboxylates	$R(OCH_2CH_2)_nOCH_2COO^- M^+$
Anionic groups connected through amide links	
Alkanolamide sulphates	$RCONHCH_2CH_2OSO_3^- M^+$
Taurines	$RCONHCH_2CH_2SO_3^- M^+$
Sarcosinates	$RCON(CH_3)CH_2COO^- M^+$
Anionic groups connected through amidine links	
Imidazole sulphates	

The discovery of this discontinuity and the reason for it were first described by McBain[5] in the 1920s and there has been a considerable volume of work on the subject since then (see Moillet *et al.*[1] and Schwartz *et al.*[2] on micelles and also Hartley[6]).

McBain postulated that surface tension fell as the concentration of single anions increased (for instance $C_{12}H_{25}OSO_3^-$ in the example given) until at the CMC the single ions began to associate into groups which he called micelles. These micelles may be in the form of spheres of molecular size, in which the hydrophobic tails of the anions are oriented to the centre of the sphere, while the

Table 33.2 Cationic Surfactants
R denotes a hydrophobic chain usually of 12 to 18 carbon atoms or an aromatic ring. X represents a suitable anion, usually chlorine or bromine.

Simple quaternary ammonium salts in which the nitrogen is attached directly to the hydrophobic unit	
Alkyltrimethyl ammonium salts	$R\overset{+}{N}(CH_3)_3\ X^-$
Dialkyldimethyl ammonium salts	$RR^1\text{—}\overset{+}{N}(CH_3)_2\ X^-$
Alkyldimethylbenzyl ammonium salts	$R\overset{+}{N}(CH_3)_2\ X^-$ $\vert$ $CH_2C_6H_5$
Ethoxylated alkyldimethyl ammonium salts	$R\text{—}\overset{+}{N}(CH_3)_2\ X^-$ $\vert$ $(OCH_2CH_2)_n$
Cationic group separated from the hydrophobic group	
Quaternized amides of ethylenediamine	$RCONHCH_2CH_2\overset{+}{N}(CH_3)_3\ X^-$
Quaternized amides of polyethyleneimine	$RCONH(CH_2CH_2N)_nCH_2CH_2\overset{+}{N}(CH_3)_3$ $\vert$ $CH_3\ X^-$
Cationic group located in a heterocyclic ring	
Alkyl pyridinium salts	
Alkyl morpholinium salts	
Alkyl imidazolinium salts	
Non-nitrogenous cationic surfactants	
Sulphonium salts	$R\text{—}\overset{+}{S}(CH_3)_2\ X^-$
Phosphonium salts	$R\text{—}\overset{+}{P}(CH_3)_3\ X^-$
Dicationic surfactants	
Quaternized diamine salts	$R\text{—}\overset{+}{N}(CH_3)_2CH_2CH_2\text{—}\overset{+}{N}(CH_3)_3\ 2X^-$

hydrophilic heads are at the outer surface. Thus a spherical micelle of sodium dodecyl sulphate would consist of a group of $C_{12}H_{25}$ tails pointing towards the centre of the sphere, with OSO_3^- heads at the surface. This micelle would correspond very roughly to a droplet of dodecane of molecular size. In fact, micelles do have the property of dissolving water-insoluble organic matter. This phenomenon is called solubilization and is one of the characteristics of surface-active agents important to the cosmetic chemist.

Table 33.3 Nonionic Surfactants
R denotes a hydrophobic chain usually of 12 to 18 carbon atoms.
n is a whole number.

Alkanolamides	
Fatty acid alkanolamides	$RCONHCH_2CH_2OH$ (ethanolamides)
Fatty acid dialkanolamides	$RCON(CH_2CH_2OH)_2$
Polyethyleneglycol derivatives	
Alkyl polyglycol ethers	$R(OCH_2CH_2)_nOH$
Alkyl aryl polyglycol ethers	$RC_6H_4(OCH_2CH_2)_nOH$
Polyglycol esters	$RCO(OCH_2CH_2)_nOH$
Thioethers	$RS(CH_2CH_2O)_nH$
Polyethyleneimine derivatives	
Alkylpolyethyleneimine	$R(NHCH_2CH_2)_nNH_2$
Polyethyleneimine amides	$RCONH(CH_2CH_2NH)_nH$

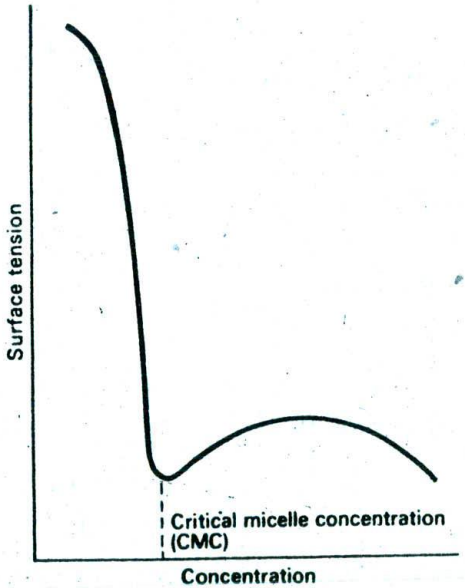
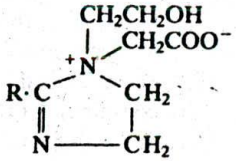


Figure 33.1 Typical curve of surface activity versus concentration for a surface-active agent

The properties of surface-active agents can be described very broadly in terms of Figure 33.1. As surface tension falls, foaming and wetting properties are usually increased. A fall in surface tension is usually accompanied by a fall in interfacial tension which gives better emulsifying and detergent properties. Finally, at concentrations above the CMC, all surface-active agents have some solubilizing properties. These properties all overlap to some degree.

Table 33.4 Ampholytic Surfactants
R denotes a hydrocarbon chain of 12 to 18 atoms.

Alkylamino acids	
Alkyl β-aminopropionates	$R\overset{+}{N}H_2CH_2CH_2COO^-$
Betaines	$R\overset{+}{N}(CH_3)_2CH_2COO^-$ and $R\overset{+}{N}(CH_3)_2CH_2CH_2COO^-$
Acylamino acids	
Acyl β-aminopropionates	$RCO\overset{+}{N}H_2CH_2CH_2COO^-$
Acyl peptides	$RCO\overset{+}{N}H_2C(R')CONHCH(R'')COO^-$
	R′ and R″ = low molecular weight alkyl group
Alkyl imidazolines	

Selection and Use of Surface-active Agents

Detergency

Detergency is a complex process which involves the wetting of a substrate (hair or skin), the removal of greasy soiling matter, the emulsification of the removed grease and the stabilization of the emulsion.

For skin cleansing, soap is still an excellent detergent. Custom dictates that a high level of foam is necessary, though it performs no function. Increased foaming can easily be achieved by superfatting with long-chain fatty acids (as in shaving soaps).

Hair washing is more complex and here foam volume does appear to play some part. Sodium lauryl ether sulphate (SLES) is a common component of shampoos, and foaming is frequently enhanced by the addition of alkanolamides. Ampholytic surface-active agents are used for specialized shampoos.

Wetting

All surface-active agents have some wetting properties. Short chain (C_{12}) alkyl sulphates, alkyl ether sulphates and alkyl aryl sulphonates are all commonly used.

Foaming

See detergency. High foam volume and stable foams are generally achieved by the use of SLES reinforced by an alkanolamide.

Emulsification
Usually a good emulsifying agent requires a slightly longer hydrophobic unit than does a wetting agent. Soap is still used as an emulsifying agent in cosmetic products, very often because of ease of preparation. If a fatty acid is incorporated in the oil phase and the alkali in the aqueous phase, then stable oil-in-water emulsions are easily formed *in situ* by simple mixing. Water-in-oil emulsions (such as in certain hair creams) are frequently stabilized by calcium soaps.

Nonionic surface-active agents are also of value in emulsions.

The theoretical basis of emulsification, choice of emulsifiers and methods of forming stable emulsions are considered in detail in Chapter 38.

Solubilization
All surface-active agents above the CMC have solubilizing properties. This is important when it is required to incorporate a perfume or an insoluble organic component into a clear product; for example a shampoo. Soaps, alkyl ether sulphates and indeed most surface-active agents have been used for this purpose. It is of course necessary to use high concentrations to give good solubilization.

All the above properties may be modified by the presence of electrolytes. In general electrolytes tend to lower the CMC and this should improve solubilization. They may also tend to break emulsions and in general electrolytes should not be added to cosmetic products containing surface-active agents until their effects on surface-active properties have been fully checked.

Other Properties
In addition to the surface-active properties listed, some surface-active molecules have special features.

All cationic products adsorb strongly at protein and other negatively charged substrates. They are thus used to modify the surface of a substrate, for example to improve the feel and appearance of hair. Cationics have some antimicrobial properties also and may be used as components of special shampoos and of mouthwashes (for example chlorhexidine) (Schwartz *et al.*,[2] p. 204).

Sodium N-lauroyl sarcosinate is known to inhibit the enzyme *hexokinase* (which is involved in the glycolytic breakdown of sugars in the mouth) and has been used in toothpastes.

Different surface-active agents should not be mixed in a product without prior testing, as one may modify the behaviour of another. Cationics and anionics should not, of course, be mixed as they give rise to the formation of a large cationic–anionic salt which is usually insoluble. (This is in fact the basis of the analytical method for estimating surface-active agents.) Even anionics can have an effect on each other; for example, the foam produced by SLES can easily be destroyed by soap (both anionic). This property is made use of in the formulation of low foam detergents.

General
There is no short cut to the selection of a particular surface-active agent for a particular end use. The measurement of surface tension, interfacial tension, foam volume, detergency, wetting, emulsifying power, etc., are all useful

indicators of surface activity, but none will predict precise requirements. In particular, behaviour under laboratory conditions may not be paralleled by behaviour of a product in use. For example, foam volume in a shampoo is considerably modified when tested in the presence of grease. Products containing surface-active agents should, therefore, always be tested under the conditions in which they will be used.

Biological Properties of Surface-active Agents

By definition surface-active agents are adsorbed at surfaces and may, therefore, modify surfaces. It is not surprising to find that as a consequence they may have biological effects. All cosmetic products containing surface-active agents should be checked rigorously to ensure that they do not have harmful effects on users.

Dermatological Effects

Surface-active agents wet the skin and may remove grease from the surface of the skin. When wrongly used they may create chapping, cracking and dryness of the skin. The C_{12} moiety seems particularly active in this respect and the C_{12} sulphate, for example, is used to create chapping artificially. Fortunately the effects are easily reduced by mixture with sulphates of other chain length, by addition of ethylene oxide (as in SLES) and by other means.

Cationic surface-active agents are strongly adsorbed on protein surfaces and care should be taken before cationics are incorporated in products which may come into contact with the eyes or the mouth.

In general, all cosmetic products containing surface-active agents should be patch tested (and if appropriate eye-tested) to ensure that they produce no adverse reaction.[7–10]

Biodegradation

The increasing use of synthetic detergents in place of soap in domestic washing has led to problems in sewage works because certain synthetic detergents are not broken down by sewage bacteria. The use of surface-active agents in the cosmetics industry is very small compared with the use in domestic washing. Nevertheless it is good practice to use only biodegradable surface-active agents. In some countries this is compulsory.

Branched-chain alkyl aryl sulphonates are not biodegradable, but the corresponding straight-chain compounds are, as are all soaps and alkyl sulphates. Most manufacturers of surface-active agents have details of the biodegradability of their products.

A Standing Committee has been reviewing the position in Britain for a number of years.[11]

Toxicological Effects

Surface-active agents are not, as a class, compounds of high toxicity. Nevertheless, since they may be ingested either accidentally or from a toothpaste or mouthwash, it is wise to check oral toxicity of cosmetic products containing them.

Of the products, cationics are the most toxic and have LD_{50} values of the magnitude of 50–500 mg per kg body weight; anionics are roughly in the range 2–8 g per kg and nonionics range upwards from about 5 g per kg[12] (and see Schwartz *et al.*,[2] p. 368). Cosmetic products containing surface-active agents should therefore be reasonably safe from toxic hazards.

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Chapter Thirty-four

Humectants

Introduction

Humectants are hygroscopic materials that have the property of absorbing water vapour from moist air until a certain degree of dilution is attained. This dilution depends on the character of the humectant used and the relative humidity of the surrounding air. Equally, aqueous solutions of humectants can reduce the rate of loss of moisture to the surrounding air until equilibrium is attained.

Humectants are added to cosmetic creams, particularly of the oil-in-water type, to reduce drying out of such creams on exposure to air. In addition the hygroscopic properties of the film of humectant which remains on the skin on application of the product may be an important factor in influencing the texture and condition of the skin.

A humectant helps to provide control in use by reducing the rate at which water disappears and viscosity decreases. It is believed to minimize 'balling' and 'rolling' of a product in use.[1]

Drying Out

Drying out of a cosmetic product may occur at any time between manufacture and final use by the consumer. It is determined by the temperature of the product, its degree of exposure to air and the relative humidity of the air to which it is exposed. It is essentially a rate process which proceeds towards the equilibrium state in which the water vapour pressure of the product is equal to that of the surrounding air.

The nature of the container in which the product is packed, and particularly the means of closure, are clearly vital in preventing drying out on storage. With an efficient closure, the humectant is of less importance since there is only a small space above the product to be saturated with water vapour.

In the case of emulsion products the type of emulsion is critical. Water-in-oil emulsions lose water at a much lower rate than oil-in-water emulsions, because of the lower water content and the fact that the external phase is oil. Oil-in-water creams are very difficult to maintain in a factory-fresh state even with a screw cap and compressible wad.

Toothpaste packed in a metal tube and with a screw cap presents a slightly different problem. The product will not normally dry out if the cap is kept in position, but if the cap is left off after use the drying out at the nozzle can cause blocking of the orifice. This can be serious in pressure-packed products where there is no easy means of clearing the obstruction. Fortunately, toothpastes can

tolerate high concentrations of humectant and a level of 30 per cent of glycerol is not unknown.

Humectants certainly do reduce drying out, as is shown by published evidence,[2,3] but their effect should not be exaggerated. The concentration of humectant in the water phase of a typical cosmetic product is normally much too low for it to be in equilibrium with average atmospheric humidity. All that the humectant can do is to reduce the rate of water loss to the atmosphere and this effect can and should be reinforced with an effective pack closure.

Griffin, Behrens and Cross[4] relate the factors of hygroscopicity and environment, and summarize the properties of the ideal humectant (Table 34.1). No humectant totally satisfies all these criteria and the final choice of humectant is usually a compromise dictated chiefly by the requirements of the product of which the humectant is a part.

Table 34.1 Properties of the Ideal Humectant (after Griffin *et al.*[4])

Hygroscopicity	The product must absorb moisture from the atmosphere and retain it under normal conditions of atmospheric humidity.
Humectant range	Within the normal r.h. range, change of water content should be small in relation to r.h. changes.
Viscosity	A low-viscosity humectant is easily mixed into a product, but conversely a high viscosity helps to prevent creaming or separation of emulsions, or settling of suspensions.
Viscosity index	The viscosity–temperature curve should be relatively flat.
Compatibility	The humectant should be compatible with a wide range of raw materials; solvent or solubilizing properties are desirable.
Colour, odour, taste	Good colour, odour and taste are essential.
Toxicity	The humectant should be non-toxic and non-irritant.
Corrosion	The humectant should be non-corrosive to normal packing materials.
Stability	The humectant should be non-volatile and should not solidify nor deposit crystals under normal temperature conditions.
Reaction	The humectant should preferably be neutral in reaction.
Availability	Humectants should be freely available and should be as inexpensive as possible.

Types of Humectant

There are three general classes of humectant: inorganic, metal–organic and organic.

Inorganic Humectants

Calcium chloride is typical of inorganic humectants, which are quite efficient but which fail badly on corrosion and compatibility. They find only limited use in cosmetic products.

Metal–Organic Humectants

The principal metal-organic humectant is sodium lactate which has, in fact, greater hygroscopic powers than glycerin. However, it is incompatible with some raw materials, can be corrosive, has a pronounced taste and may discolour. It has not been widely used in cosmetics but has been recommended for use in skin creams,[5] particularly because lactates occur naturally in the body and there is no risk of toxicity or dermatitis. The problem of pH can be overcome by admixture with lactic acid which is also fairly hygroscopic. Buffered solutions can be obtained between pH 7·1 and pH 2·2 at 5 per cent sodium lactate/lactic acid.

Organic Humectants

Organic humectants are the most widely used type; they are usually polyhydric alcohols, their esters and ethers. The simple unit is ethylene glycol and by progression up the series the most common products are:

Glycerol (trihydroxypropane)
Sorbitol (hexahydrohexane)

A series can be built up by the addition of ethylene oxide to a basic unit or just to itself. This produces, for example, polyethylene glycols of varying molecular weight which often have useful cosmetic properties of their own. The multiple ether linkages reduce hygroscopic properties which depend primarily on the ratio of —OH groups to C atoms.

In general the type of organic humectant used is determined primarily by availability. The soap industry inevitably produces glycerol as a by-product and this can also be synthesized from petroleum building blocks. This makes for availability and price stability and glycerol is probably the most popular humectant used in cosmetics though this accounts for only a small percentage of total use.[6,7]

Sorbitol (in the form of 70 per cent syrup) has recently replaced or partially replaced glycerol in many cosmetic products. The replacement increases the water content of the final product. This is not important in most cosmetic products, but it may be vital in toothpastes which normally have a low water content.

Thus the compounds most generally used in cosmetic products for hygroscopic purposes are:

Ethylene glycol
Propylene glycol
Glycerol
Sorbitol
Polyethylene glycol

Hygroscopicity

The method most frequently used to determine hygroscopic qualities is to construct a curve of relative humidity of atmosphere against humectant concentration in equilibrium. This is done by exposing small weighed amounts of solutions of known composition in atmospheres of controlled humidity and

weighing periodically. The controlled humidities can be achieved in small desiccators charged with crystals wetted with their own saturated solutions (Table 34.2). Other humidities in the lower range are best achieved over sulphuric acid solutions of known concentration; the humidities are given in standard tables.

It is both unnecessary and inadvisable to continue weighing until equilibrium is attained because this can be a lengthy process, and moreover the more concentrated solutions do not mix well without stirring. After one, or at most two weighings at intervals of a few hours, at each humidity there will be found a division between the more concentrated solutions which gain weight by attracting water and the more dilute solutions which lose water. It is within this gap that the required concentration in equilibrium with the particular humidity lies and a second experiment with solutions covering the smaller range of concentrations will pinpoint the exact value.

Figures taken from curves for ethylene glycol, glycerin, sorbitol, propylene glycol, 2,3-butylene glycol and sodium lactate determined by a similar method to that described are given in Table 34.3.

The extensive survey of Griffin, Behrens and Cross[4] of many hygroscopic materials included a comprehensive table which is reproduced in part as Table 34.4. They also revised a graphical method proposed by Livengood[8] for choosing humectants for a desired equilibrium hygroscopicity and for calculating the effect of combinations of humectants. Their revised form of the Livengood graph, with a corrected family of curves over a limited range where the relationship holds with an accuracy of about ±5 per cent water for most organic humectants, is shown in Figure 34.1.

To use the graph the water content of the chosen humectant at 50 per cent r.h. is determined by reference to Table 34.4. This value is then transferred to the 50 per cent relative humidity ordinate on Figure 34.1. A curve is drawn through this point parallel to the nearest curves on the graph. The appropriate

Table 34.2 Suitable Crystals for Establishing Atmospheres of Controlled Humidity

	Relative humidity (%)
$K_2Cr_2O_7$	98
$Na_2SO_4.10H_2O$	94
$BaCl_2.2H_2O$	88
NaCl	75
KI	71
$NaNO_2$	66
$NaBr.2H_2O$	58
$NaHSO_4.H_2O$	52
$Na_2Cr_2O_7.2H_2O$	52
KCNS	47
$CaCl_2.6H_2O$	33
CH_3COOK	20

Table 34.3 Concentration Related to Relative Humidity for Various Humectants

	Ethylene glycol	Glycerin	Sorbitol	Propylene glycol	2,3-Butylene glycol	Sodium lactate
Relative humidity (%)	**Concentration of humectant (%)**					
90	40	35	49	35·5	44	24
80	57	50	65	58	59	36
70	69	62	73	66	70	44
60	77	71	78	75	79	48
50	84	78	83	83	85	52
40	89	84	—	91	91	57
30	93	89	—	96	94	64
20	96	94	—	99	96	—
10	98	97	—	99	97	—
Humectant (%)	**Relative humidity (%)**					
10	98	97	98·5	97·5	97	96
20	96	95	97	94	96	92·5
30	93	92	95	93	94	86
40	90	87	93	91	91	76
50	85	80	89·5	86·5	85	55
60	78	72	84	77·5	79	35
70	69	61	73	66	70	25
80	57	48	57·5	54	59	22
90	38	28	57·5	42	44	—

equilibrium moisture content can then be read off the curve for humidities between 25 and 75 per cent.

Blends of humectants do not always show hygroscopicities exactly in accord with the arithmetic average of their individual hygroscopicities. But, in general, it is sufficiently accurate for practical purposes to consider the individual quantities of humectant present as acting independently of each other.

However, the moisture content at equilibrium is far from being the whole story. It will be seen from Table 34.3 that to be in equilibrium with normal humidities of 70–75 per cent the amount of humectant in the aqueous phase needs to be of the order of 60–70 per cent, which is clearly impractical for various reasons.

Bryce and Sugden[3] confirmed the findings of Griffin *et al.*[4] that a humectant could show different efficiencies at different concentrations and, in addition to minima, reported a maximum efficiency in the region of 1 per cent humectant in a typical vanishing cream formula. This can only be attributed to surface-active effects which predominate at very low concentrations but become insignificant at higher concentrations where hygroscopic effects predominate.

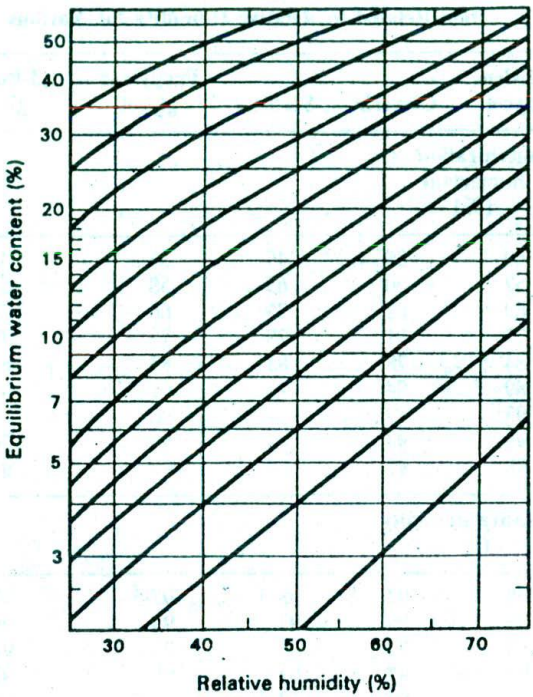

Figure 34.1 Humectants—estimation of equilibrium moisture content from 50 per cent r.h. value (Courtesy Atlas Powder Co. and *Journal of the Society of Cosmetic Chemists*[4])

Thus it may well be considered that the levels, particularly of glycerin, traditionally used are a reasonable compromise between optimum performance in terms of other properties.

Water Loss from Oil-in-water Emulsions

Griffin, Behrens and Cross[4], prepared two similar oil-in-water creams, one emulsified with soap, the other with nonionic materials, with different levels of propylene glycol, glycerin or sorbitol (0, 2, 5, 10, 20 per cent). The different creams were exposed at 30, 50 and 70 per cent humidities and the weight loss monitored for 48 hours; the weight loss was about 10 per cent of the cream, which is from 10–15 per cent of the net water content and adequate for the estimation of rates of loss. The fact that the nonionic cream lost weight slightly faster was attributed to the surface crust which formed on the soap-based cream and retarded the water loss but, at the same time, made the cream unfit for use as a cosmetic. The results, given in Table 34.5, show discrepancies which are attributed to changes in texture and consistency, and crust formation, which are not wholly dependent on water loss but are, in addition, a function of the type of emulsifier used.

Table 34.4 Physical Properties of Humectants
* Per cent w/w solids. † 25°C. —Data not available. X Crystalline.

Humectant	Freezing point (°C) vs concentration*				Viscosity (cP) vs concentration* at 20°C				
	100%	75%	50%	25%	100%	85%	70%	50%	25%
Ethylene glycol	−11·5[10]	−65[5]	−37[5]	−11[5]	19[5]	12[5]	7[5]	4[6]	1·8[5]
Diethylene glycol	−10·45[6]	—	−28[5]	−8[5]	38[5]	17[5]	9·5[5]	4·6[6]	2·0[5]
Triethylene glycol	−5[9]	—	−24[5]	−6[5]	45[5]	—	20[6]	6·8[6]	2·3[5]
							(75%)		
Polyglycol 400	4 to 10[12]	—	—	—	—	—	43[3]	14[4]	1·5[3]
Polyglycol 600	20–25[12]	—	—	—	—	—	—	14[4]	1·5[3]
'Carbowax' 1000	35–40[12]	—	—	—	solid[3]	—	—	21[4]	1·5[5]
'Carbowax' 4000	50–55[12]	—	—	—	solid[3]	—	solid[3]	—	17[3]
Propylene glycol	—	—	−33[5]	−10[5]	55[5]	21[5]	11·2[5]	5·2[6]	2·0[5]
Dipropylene glycol	—	—	—	—	—	—	—	—	—
Glycerin	17·0[8]	−29·8[8]	−23·0[8]	−7·0[8]	1499[11]	112·9[11]	22·94[4]	6·050[11]	2·095[11]
Polyoxyethylene glycerin	—	—	—	—	—	—	—	—	—
Alpha methyl glycerin	—	—	—	—	viscous liquid[7]		—	—	—
Xylitol	—	—	—	—	—	—	—	—	—
Sorbitol (ARLEX) (85% soln.)	—	—	—	—	—	3500†	110†	9†	2†
Sorbitol (SORBO) (70% soln.)	—	—	—	—	—	—	110†	9†	2†
Mannitol	166	—	—	—	—	—	—	—	—
Sorbitan (A-810)	—	—	—	—	—	1000†	—	—	—
Sorbide (A-815)	—	—	—	—	—	200†	—	—	—
					(95%)				
Polyoxyethylene sorbitol (G-2240)	—	—	—	—	975	250†	53†	12†	—
Polyoxyethylene sorbitol (G-2320)	—	—	—	—	—	—	—	—	—
Glucose	—	—	—	—	—	—	—	—	—
Propylene glycol glucoside (A-850)	—	—	—	—	—	—	—	—	—
Triethanolamine	21·2[1]	−40	−14[1]	−2[1]	1013[1]	135[1]	45[1]	10[1]	4[1]
Sodium lactate	—	—	—	—	—	—	—	—	—
Triethanolamine lactate	—	—	—	—	—	—	—	—	—
Urea	132·7	—	—	—	—	—	—	—	—

Table 34.4 (*cont.*)

	Viscosity (cP) vs temperature (°C:100%)					Equilibrium hygroscopicity (% solids vs % r.h.)		
	0	25	50	75	100 (120)	30	50	70
Ethylene glycol	50[5]	17[5]	6[5]	2·0[5]	0·35[2]	88	75+	56−
Diethylene glycol	100[5]	28[5]	8[5]	5[5]	—	90	82	60[4]
Triethylene glycol	—	35[5]	14[5]	7[5]	—	91+	84	63[4]
Polyglycol 400	solid[3]	—	—	—	—	95−	89	79+
Polyglycol 600	solid[3]	—	—	—	—	96−	90	80−
'Carbowax' 1000	solid[3]	solid[3]	—	—	—	98−	92	—
'Carbowax' 4000	solid[3]	solid[3]	solid[3]	—	—	99+	99−	96
Propylene glycol	—	40[5]	12·5[5]	5[6]	—	91	82	68
Dipropylene glycol	—	—	—	—	—	96[4]	89[4]	77[4]
Glycerin	solid[8]	945[8]	—	—	—	89+	80	65+
Polyoxyethylene glycerin	—	—	—	—	—	94	87+	76+
Alpha methyl glycerin	—	—	—	—	—	—	—	—
Xylitol	—	—	—	—	—	92	84−	71−
Sorbitol (ARLEX) (85% soln.)	—	—	—	—	—	96+	87+	75+
Sorbitol (SORBO) (70% soln.)	—	—	—	—	—	X	X	75−
Mannitol	—	—	—	—	—	X	X	X
Sorbitan (A-810)	—	—	—	—	—	95	87−	75+
Sorbide (A-815)	—	—	—	—	—	97	91+	80
Polyoxyethylene sorbitol (G-2240)	—	—	—	—	—	—	88−	—
Polyoxyethylene sorbitol (G-2320)	—	—	—	—	—	91−	90+	—
Glucose	—	—	—	—	—	94	88+	79
Propylene glycol glucoside (A-850)	—	—	—	—	—	89−	84+	77−

		(35°C)						
Triethanolamine	—	280[1]	115[1]	32[1]	17[1]	92[9]	80[9]	52
Sodium lactate	—	—	—	---	—	84–	68–	50–
Triethanolamine lactate	—	—	—	---	—	—	81–	—
Urea	—	—	—	--	—	X	X	(80%) 51

[1] Carbon and Carbide Co., *Amines*, New York, 1944.
[2] American Maize Products Co., *Average Temperature and Humidity* (twelve maps—months of year), New York, 1939.
[3] Carbon and Carbide Co., *Carbowaxes*, New York, 1946.
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Table 34.5 Water Loss from Soap-based and Nonionic-based Oil-in-water Emulsions[4]

	r.h.	Sorbitol	Glycerin	Propylene glycol
Soap-based o/w cream	30%	Concs. as low as 2% provide protection against drying out.	At least 5% required to protect. Below this level the cream loses more than in absence of humectant.	At least 10% required to protect. Below this level, greater loss than in absence of humectant.
	50%	Inhibited water loss at all concentrations.	None of the concentrations used afforded protection against drying out and at lower concentrations the creams lost more than in absence of humectant.	As for glycerin
	70%	Inhibited water loss at all concentrations.	Ineffective at 10% or less	Ineffective at 5% or less
Nonionic-based o/w cream	30%	All concentrations of all humectants inhibited weight loss. Order of effectiveness at 2%, best first: sorbitol, propylene glycol, glycerin. Same order persisted at 5% and 10% but to lesser degree and differences had almost disappeared at 20%.		
	50%	All concentrations of all humectants inhibited weight loss with no appreciable difference between humectants at equivalent concentrations.		
	70%	All concentrations of all humectants inhibited weight loss with no appreciable difference between humectants at equivalent concentration.		

Water Loss from Water-in-oil Emulsions

In water-in-oil creams the aqueous phase is completely enveloped in oil, and water loss will not be as great as with oil-in-water creams. Nevertheless it is generally believed that the addition of about 5 per cent humectant on the cream or 8 per cent on the water phase may play a part in reducing water loss. Griffin, Behrens and Cross, however, made the eminently sensible suggestion that a humectant for water-in-oil cream should be selected more for its desirable properties when left on the skin than for the reduction of moisture loss which is adequately controlled if the product is an efficient water-in-oil emulsion.

Stability of Emulsions

Experiments carried out by deNavarre[9] indicate that the polyols glycerin, sorbitol and propylene glycol were not interchangeable in that in a water-in-oil cream the sample containing propylene glycol and the control sample had the greatest stability while that containing glycerin showed the most oil separation.

Conversely, in an oil-in-water emulsion the sample containing glycerin and the control remained fluid while those containing propylene glycol and sorbitol would not flow after storage. On the basis of such observations it would appear that glycerin promoted the formation of an oil-in-water emulsion while propylene glycol favoured a water-in-oil emulsion, their use in the wrong types leading to instability. Sorbitol was apparently midway, in such properties, between these other two humectants. Cessna, Ohlmann and Roehm[10] also reported that the three polyols glycerin, propylene glycol and sorbitol undoubtedly affected the fundamental emulsion properties of the preparations tested in different manners, since glycerin and propylene glycol appeared to have opposite effects in emulsions of the same type.

The humectant will affect stability through its viscosity and in addition by its chemical nature. It is possible that in some complex systems, especially those containing monoglycerides, glycerin can positively promote stability.

Safety

The three humectants widely employed in the cosmetic and toilet industry at the present time—and which have been discussed in this chapter—namely, glycerin, sorbitol and propylene glycol, are non-toxic and dermatologically innocuous.

Ethylene glycol is not considered safe, since it is oxidized in the body to oxalic acid and any absorption through the skin might lead to renal calculus; for the same reason diethylene glycol is considered toxic. The mono-ethyl ether of diethylene glycol (Carbitol) has been widely used in cosmetic and toilet preparations and because of its ether grouping does not constitute, so far as is known, a hazard when used externally in cosmetic and toilet preparations.

Glycerin, in particular, has been questioned because of the hygroscopicity of pure glycerol which had been considered to be capable of drawing water from the skin.[11,12] This may be irrelevant since the concentrations necessary to produce this effect are never used in practice and the equilibrium is always approached from the other side.

Skin Moisturizing

This has been discussed in general in Chapter 4. In the present state of knowledge, it is not possible to define satisfactorily the role of humectants in skin care.

It would appear that the presence of a humectant may be expected to stabilize the water content of the residual film from a cream on the skin and prevent excessive drying out. However, the manner in which adjustment is made with changes in the ambient humidity, and whether the skin is dried or moistened, will depend on the relative transfer rates of water between the atmosphere and the film and the skin. The measurement *in vivo* of transepidermal water loss is discussed by Idson.[13]

On balance, therefore, the traditional belief in the use of humectants in skin products both for the probable benefit to the product while it remains in its container, and the possible benefit to the skin during use, appears to be justified.

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Chapter Thirty-five

Antiseptics

Introduction

An examination of products in current use indicates that a substantial proportion of toilet preparations applied to the body for normal hygienic and cosmetic purposes are formulated as medicated products which range from soaps and shampoos to mouthwashes and toothpastes.

Antibacterial agents are included in toilet preparations mainly to alleviate commonly occurring conditions such as halitosis, body odours and minor skin infections including secondary infections associated with acne. Although there is inevitably some overlap, these products should be distinguished from pharmaceutical products used for treatment of pathological conditions which may contain antibiotics and other agents not normally considered suitable for general purposes of hygiene.

The major types of personal hygiene product, with examples of antibacterial agents they may contain, are given in Table 35.1 which also includes various pharmaceutical and cosmetic products sometimes used for specific purposes such as 'first aid' and treatment of minor skin ailments and for 'hand degerming' by medical personnel.

The terms 'antiseptic' and 'germicidal' are predominantly used to describe preparations applied to living tissue to prevent infection although 'germicidal' is often applied to antibacterial soap bars. Although the term 'disinfectant' is more correctly used to describe preparations for treatment of inanimate objects such as floors, toilets, drains and so on, the term 'skin disinfectant' is often applied to products used by medical and other personnel to prevent transmission of infection in hospitals, the food industry and other high risk areas.

Use of antiseptics in toilet preparations should be distinguished from use of preservatives, in that the former are expected to render the product active against micro-organisms present on the skin or scalp or in the mouth, whereas the function of preservatives (often the same antibacterial agent) is to maintain the product in a satisfactory condition during its shelf life and use.

The benefits of including antimicrobial agents in toilet preparations have in recent years been seriously questioned with the result that health and welfare authorities in many parts of the world have made recommendations or introduced laws governing the use of certain germicides. These usually limit the choice available to manufacturers, and in some cases specify the concentration considered safe. These laws and recommendations differ in different countries and moreover they are subject to change as evidence accumulates about the safety of individual antiseptics in relation to the benefits of their use—hexachlorophene, until recently the most widely used of all germicides, is an example.

Table 35.1 Antibacterial Agents Commonly Used in Toilet Preparations

Type of product	Antibacterial agents
Antibacterial soap bars	Coal tar TCC TBS Irgasan DP300 (Hexachlorophene)
General disinfectants and antiseptics	Chlorhexidine/cetrimide Chloroxylenol
Formulated emulsions, etc.	Chlorhexidine Irgasan DP300 Iodophors (Hexachlorophene)
Antiseptic creams and ointments	Chlorhexidine Cetrimide Resorcinol Phenol Sulphur etc.
Antidandruff and medicated shampoos	Zinc pyridinethione Selenium sulphide Coal tar Irgasan DP300 (Hexachlorophene)
Deodorants and antiperspirants (including feminine hygiene products)	Zinc phenolsulphonate Chlorhexidine Irgasan DP300 Quaternary ammonium compounds (Hexachlorophene)
Toothpastes and mouthwashes	Quaternary ammonium compounds Chlorhexidine (Hexachlorophene)

In 1974 the US Food and Drug Administration published a report based on an evaluation of existing data on the use of antimicrobials in soap and cosmetics. The report classified antimicrobial agents for topical use into three categories:

(1) safe and effective,
(2) not safe and/or effective and
(3) insufficient evidence.[8]

Microbial Flora of the Body

The normal flora of the body surface comprises two distinct groups of organisms—the resident flora and the transient flora. Resident organisms that

proliferate on the skin are mainly non-pathogenic, that is, Gram-positive staphylococci, micrococci and corynebacteria, although in moist areas such as the axilla and groin Gram-negative organisms such as acinetobacter may be present. It has been estimated that, for 35–50 per cent of the population, the resident skin flora also includes *Staphylococcus aureus* although a report by Armstrong-Esther *et al.*[9] indicates that, for many of these subjects, presence of *Staph. aureus* is only intermittent and that a much higher proportion of the population harbours this organism occasionally.

It should be noted that the population of bacteria varies considerably on different parts of the body; the hair, face, axilla and groin harbour the greatest numbers of organisms, whereas colonization of more exposed and dry areas such as legs, arms and hands is relatively less extensive. Most resident organisms are found on the superficial skin surface but 10–20 per cent of the total flora is concentrated in hair follicles, sebaceous glands and so on where lipid and superficial cornified epithelium make their removal difficult. It is generally accepted that skin washing is relatively ineffective in removal of resident organisms and that significant reductions in skin flora can only be achieved by application of antibacterial agents.

Fortunately the resident skin flora is predominantly of low virulence although minor skin infections, particularly pyogenic infections, are relatively common. More serious septic infections usually result only where organisms are introduced into the body by injury or surgical procedures.

Various areas of the body (although mainly the hands) also contain, in addition to the resident flora, transient flora consisting of contaminants picked up continuously from the environment and other body areas such as the nasal mucosa and gastrointestinal tract. This flora may contain any number of different organisms including pathogenic strains of *Pseudomonas*, *Enterobacter*, *Salmonella*, *Shigella* and *Escherichia coli*. In general, however, these transient contaminants survive for only relatively short periods owing to insufficient moisture and the presence of bactericidal substances such as fatty acids on the skin surface. In contrast to the resident flora, these organisms are only loosely attached to the skin and may be removed in substantial numbers by washing and bathing.

A more detailed treatment of the microbial flora of the human body surface is given by Skinner *et al.*[10]

Effects of Antibacterial Agents on Body Flora

From the fairly extensive investigations carried out over the past 10–20 years there is little doubt that, whereas a substantial reduction in skin flora can be achieved by washing with soap and water alone, this effect may be significantly increased by the use of antiseptics. In contrast, however, there is considerable disagreement as to whether the strength of evidence indicating that use of antiseptics for routine hygiene is associated with reduction of infection outweighs the possibility of harmful effects resulting from continual application of these agents to the skin.

It has become increasingly apparent that the effectiveness of antiseptic preparations depends not only on the properties of the antimicrobial agent but

also on the nature of the formulation, which may be a soap bar, emulsion, liquid soap or detergent formulation. A typical set of results obtained by Lilly, Lowbury *et al.*[1,2] (Figure 35.1) shows that application of chlorhexidine formulations produces rapid and immediate reduction in skin flora, whereas phenolic compounds such as hexachlorophene and Irgasan DP300 produce limited effects after a single application, maximum activity from these latter compounds being obtained only after prolonged use.

Detailed investigations illustrating the way in which the activity of a number of antibacterials *in vivo* may be affected by the nature of the formulation have been reported by Lilly, Lowbury *et al.*,[1–7] Gibson[11] and Ojajarvi.[12]

In the development of effective antiseptic toilet preparations, therefore, it is necessary that products are formulated according to the desired effect (that is, reduction in resident or transient flora) or the need for immediate or progressive and prolonged reduction in bacterial flora. Medicated toilet preparations used for routine washing and bathing are intended largely to protect the individual against minor skin infections by both resident and transient bacteria and to assist in the control of conditions such as body odour and halitosis, whereas routine handwashing associated with toilet visits, food hygiene and the handling of

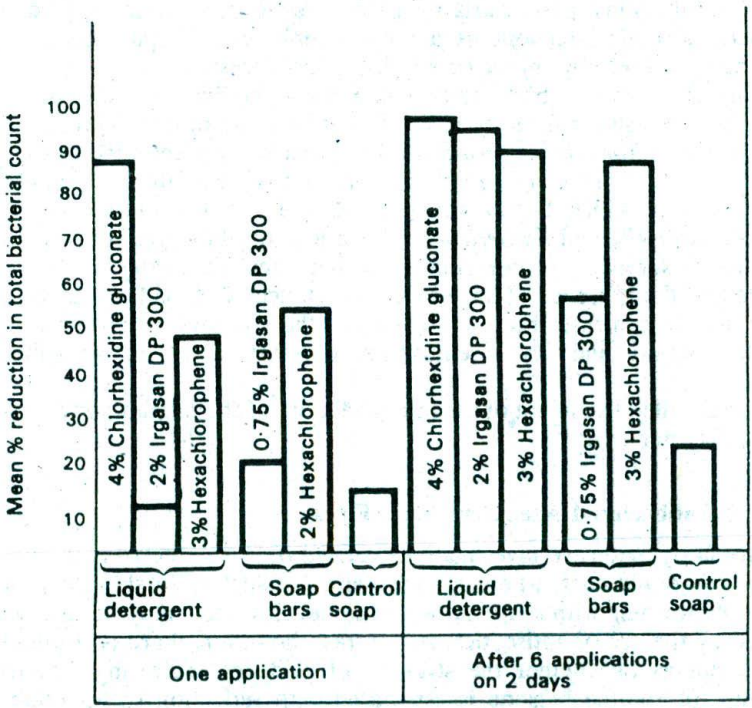


Figure 35.1 Mean percentage reduction of bacteria on skin as determined by handwashing tests associated with use of skin disinfectants (data reproduced by kind permission of Dr H. A. Lilly, Dr E. J. Lowbury, *British Medical Journal* and *Journal of Applied Bacteriology*[1–7])

newborn infants and sick persons is intended for removal of transient organisms from the skin to prevent transmission of infection.

The use of antiseptic preparations for routine hygiene is considered below. More detailed consideration of deodorants, medicated shampoos, toothpastes, mouthwashes and baby preparations is given in Chapters 10, 24, 31, 32 and 8 respectively.

Antibacterial Soap Bars and Other Skin Degerming Preparations

Routine Hygiene Usage

Investigations by a number of workers indicate clearly that persistent reduction in skin flora may be obtained by routine use of soap bars containing salicylanilides, carbanilides, various halogenated phenols and related compounds. Percentage reduction of skin flora may be determined by standard handwashing techniques involving bacterial counts taken before and after washing with antibacterial soap over a specified period.[3,13,14] Results of a number of investigations using different antibacterial soap bars are summarized in Table 35.2.

Table 35.2 Reduction in Skin Flora with Use of Antibacterial Soaps

Antibacterial agent	No. of days of test	Reduction in microbial flora (%)	Source
Hexachlorophene 2%	2 (6 applications)	87·7	Lilly *et al.*[7]
Irgasan DP300 0·75%	2 (6 applications)	56·2	
Irgasan CF3 0·5%	3	90·0	Guklhorn[14]
Irgasan DP300 1%	3	92·0	Furla *et al.*[15]
Irgasan DP300 2%	3	95·0	
Irgasan DP300 0·6%	4	60	Ojajarvi[12]
Hexachlorophene 2%	7	81	
Bithionol 2%	7	77	
TMTD 1%	7	76	Hurst *et al.*[16]
TCC 2%	7	72	
TBS 0·5%	7	65	
TCS 0·5%	7	84	
TCC 1%	12	91·7	Roman[17]
2%	12	97·8	
Hexachlorophene 2%	28 (minimum)	63–90	Wilson[18]
TCC 2%	28	89–97	

It is suggested that the sustained effects of medicated soaps are due to the substantive properties of antibacterial agents which remain on the skin after handwashing. Methods used to test skin substantivity of antibacterial agents are described by Gibbs *et al.*[19] while studies using radioactive labelled hexachlorophene and trichlorocarbanilide are reported by Taber *et al.*[20]

Under normal conditions, the healthy person is adequately resistant to organisms present on the skin surface but minor skin infections are relatively common even in healthy families, and particularly where there are young children, and it is possible that routine use of antibacterial soap bars, medicated shampoos, etc., may assist in their control. In relation to this, a number of studies involving military personnel and prisoners[21–23] have shown reductions in incidence of pyogenic skin infections associated with routine use of antibacterial soap bars for periods of up to nine months.

Although these workers report no evidence of adverse skin reactions, various investigators have from time to time expressed concern regarding possible dermatitic effects, skin drying and other effects which might result from prolonged use of these products. Other workers have demonstrated that suppression of the normal Gram-positive skin flora by use of the various agents with more selective action against these organisms may promote colonization by Gram-negative bacteria;[21,25,26] however, this is probably of little concern compared with the significant overgrowth which may accompany antibiotic usage.[27]

Antiseptic preparations are generally used to prevent or alleviate minor skin infections in the user but there is little doubt that the body surface and particularly the hands play an important part in transmission of infection in the community.

Although removal of transient skin flora can be substantially increased by application of suitable antiseptic preparations such as liquid detergent formulations containing iodophors or chlorhexidine, which produce rapid and immediate bactericidal action,[1,4,7,12] investigations show little evidence that disinfectant usage for regular washing or for rapid 'skin degerming' before patient contact by hospital personnel is accompanied by any significant reduction in incidence of cross-infection.[28,29] It therefore appears that, although skin washing is vital in controlling dispersal of infection, disinfectant usage is probably not justified except in certain 'high risk' hospital areas and that the substantial removal of transient contamination achieved by soap and water washing[4] is adequate for most purposes of food and toilet hygiene.

Antiseptics in First Aid

Antiseptic creams or other skin disinfectants are used in first aid treatment of cuts, burns and other wounds to prevent infection during healing. They are also used for treatment of minor skin infections, particularly those associated with the face. For first aid purposes, rapid acting compounds such as iodophors, chlorhexidine and chloroxylenol products are recommended[4] although certain workers have suggested that antiseptics are unnecessary in this situation and may damage healthy skin cells, thereby delaying normal healing.

Antimicrobial Agents Commonly Used in Antiseptic Products

Space permits only an outline of the more important properties of antimicrobial agents used in antiseptic products and of investigations of their activity *in vivo*. Detailed information on studies of bacteriostatic and bactericidal activity *in vitro* may be obtained from extensive reviews by Guklhorn[14] and Block.[30]

Phenols and Cresols

A very considerable number of phenol and cresol derivatives are known to have antibacterial activity although in general these compounds are more active against Gram-positive than Gram-negative bacteria. For antiseptic purposes, concentrations of 0·1–5 per cent are used but, since many of the compounds are only sparingly water-soluble, it is necessary to use soaps or other surface-active agents to achieve concentrations sufficient for optimal activity. Although toxicity may be fairly low, many phenolics are irritant in high concentrations.

For these reasons these compounds are not much used in toilet preparations, having been largely superseded by the bisphenols, salicyanilides and carbanilides.

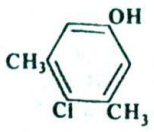
Although DCMX (2, 4-dichlor-*sym*-metaxylenol) has been investigated for use in antibacterial soap bars,[16,31–33] chloroxylenols are mainly used in antiseptics for treatment of minor injuries or in disinfectants, including pine oil disinfectants for hospital or domestic disinfection.[4]

Chlorocresol BP (PCMC, parachlorometacresol) (Figure 35.2) has similar antimicrobial power to chloroxylenol BP (PCMX, parachlorometaxylenol) although its Rideal Walker coefficient is lower. It has irritant action at high concentration and a persistent and characteristic odour demanding careful selection of perfumes in use. Like the chloroxylenols it is seldom used except as a preservative.

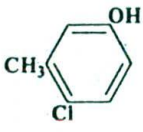
Bisphenols

Of the very large number of phenolic antiseptics that have been synthesized, the halogenated phenols are amongst the most potent. Several halogenated diphenol derivatives have gained wide usage in toilet preparations particularly because of their compatibility with soap. Of these hexachlorophene (2,2′-methylene-*bis*-(3,4,6-trichlorophenol)), dichlorophene (2,2′-methylene-*bis*-(4-chlorophenol)), bithionol (2,2′-thio*bis*-(4,6-dichlorophenol)) and Irgasan DP300 (2,4,4′-trichloro-2″-hydroxydiphenylether) (Figure 35.2) have been more widely used than others. Like other phenolics these compounds are generally more active against Gram-positive than Gram-negative bacteria and fungi. As with all the substituted phenols, since these compounds are only sparingly soluble in water, aqueous preparations are formulated to contain surface-active molecules in order to achieve satisfactory concentrations for activity. For antiseptic purposes, concentrations of 0·5–2·0 per cent are generally used. All these compounds are incompatible with cationic compounds and incompatibility of hexachlorophene with a number of anionics and nonionics has also been reported.[16,32–44]

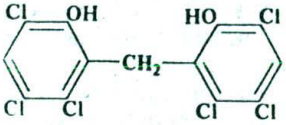
Hexachlorophene (G11) (Givaudan). The activity of soap bars, liquid soap and detergent emulsion formulations containing from 2–3 per cent hexachlorophene



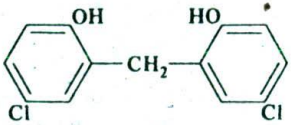
PCMX



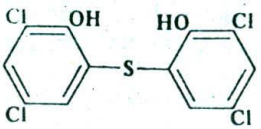
PCMC



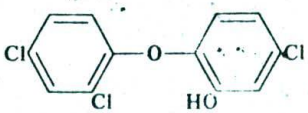
Hexachlorophene



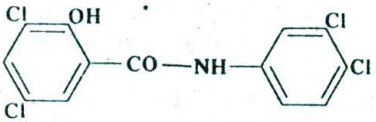
Dichlorophene



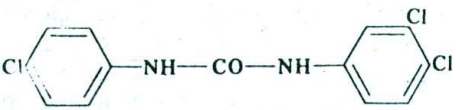
Bithionol



Irgasan DP 300



TCS



TCC

Figure 35.2 Formulae of some anionic-compatible antiseptics

has been investigated by Lilly and co-workers,[3–5,7] Gibson [illegible] Jarvi,[12] Hurst *et al.*,[16] Wilson[18] and Sprunt.[29] In general these workers show that hexachlorophene preparations have only limited activity after a single application although extensive reduction in skin flora may be demonstrated after prolonged application over several days. Lilly *et al.*[5] and Ojajarvi [illegible]ed that the immediate effects associated with a single application of 3 per cent hexachlorophene liquid soap preparation could be increased by addition of 0·3 per cent chlorocresol.

One important disadvantage associated with use of hexachlorophene is its selective activity against Gram-positive organisms with the result that Gram-negative organisms may be found growing in these products.[35] A number of investigations also indicate that prolonged use of hexachlorophene may be associated with increased skin colonization by Gram-negative bacteria.[26,36–38]

Until recently, hexachlorophene commanded wide usage in toilet preparations and was considered to have a remarkably good safety record. However, its widespread use in soaps, toothpastes, mouthwashes, deodorants, feminine hygiene products, medicated shampoos, hair cream and baby products gave rise to fears that undesirable accumulation of the germicide in the body could occur and, following a series of animal toxicity studies, the use of hexachlorophene

was restricted in several countries. Studies on the toxicity of hexachlorophene have been summarized by Kimbrough.[39]

In September 1972, however, following reported gross contamination by hexachlorophene of a baby powder associated with fatalities in a number of infants in France, the US Food and Drug Administration announced that it would limit the use of hexachlorophene to products available on prescription.[40] This followed an earlier statement of policy which permitted the use of up to 0·1 per cent of hexachlorophene as a preservative where there was no suitable alternative.

In the United Kingdom, the Committee on Safety of Medicines has recommended that medical personnel should be informed of a possible hazard in using hexachlorophene, especially with respect to infants, that products containing it should bear a cautionary label and that certain of these should be recommended for use only on medical advice.[41]

No evidence of hazard to health in man has been seen in the many years of use of hexachlorophene at recommended levels, but because of the observations in animal tests and the tragic events which occurred in France, the future of this once well respected germicide must now be regarded as uncertain.

Dichlorophene (G4) (2,2′-methylene-*bis*-(4-chlorophenol)) (Givaudan). Dichlorophene has also been used in soaps and toilet preparations but to a much lesser extent than hexachlorophene. Investigations by Lowbury *et al.*[3] indicate that use of a liquid soap preparation containing 2 per cent dichlorophene over a period of four days was less effective than 2 per cent hexachlorophene in liquid soap in reduction of resident skin flora.

Bithionol (Actamer, Vancide BL) (Hilton Davis Chemicals Co., USA). The properties of bithionol as an alternative to hexachlorophene have been discussed by Powell *et al.*[42] Although bisphenols are rarely irritant to the skin and only occasionally produce allergic reactions, evidence of photosensitization caused by bithionol has been accumulating in the last few years, and in 1968 the US Food and Drug Administration issued an order preventing the further introduction in the USA of products containing bithionol.

Irgasan DP 300 (Geigy). Irgasan is a relatively new antiseptic which is now used widely in antibacterial soap bars, skin degerming preparations, medicated shampoos and deodorant products.

Although it is very effective even at low concentrations against several Gram-negative bacteria and the usual range of Gram-positive bacteria, it has no activity against *Pseudomonas* and is relatively ineffective against fungi. For this reason it cannot be recommended as the sole preservative in products prone to microbial spoilage but, because of its action against the resident and transient bacteria on the skin, it is suitable for use in antiseptic products.

Irgasan DP 300 has been subjected to a very thorough toxicological examination and has been found to be practically non-toxic.[14,43] Animal tests have shown very low local irritant or systemic toxic effects and no sensitizing activity was observed in tests carried out on guinea-pigs. Extensive trials on humans have also

been carried out and no cases of sensitization or photosensitization have been reported.

Concentrations of 0·5–2 per cent are recommended for use in products which are rinsed from the skin after application, such as toilet soaps, bath additives, liquid shower soaps, etc. For products designed for application to the skin without removal, such as deodorant sticks, creams, aerosol sprays, intimate hygiene products, etc., concentrations of 0·05–0·2 per cent are suggested.

Irgasan DP 300 is unusual in being compatible with soaps and other anionic systems while at the same time being very effective against the Gram-negative bacteria likely to be present on the skin. Savage[44] has pointed out its value in combating the organisms responsible for certain characteristic malodours on the body, and has reported residual bacteriostatic activity on the hair against both Gram-positive and Gram-negative organisms after use of shampoos containing 0·15–0·3 per cent of Irgasan DP 300.

The activity of bar soap and a bactericidal washing cream containing respectively 0·6–0·75 per cent and 2 per cent Irgasan DP 300 has been investigated by Lilly and co-workers[2,7] and Ojajarvi.[12] Like hexachlorophene, these products produced only limited effect after a single application, optimum activity being achieved only after a period of use (Figure 35.1). Although the reduction in skin flora following prolonged usage of 2 per cent Irgasan DP 300 washing cream compared favourably with other preparations, in general activity of this antiseptic was somewhat less than that of hexachlorophene. Investigations by Furla *et al.*[15] indicate that activity of soap bar formulations can be substantially improved by increasing the concentration of Irgasan DP 300 to 1–2 per cent (Table 35.2).

Fentichlor (*Bis*-(2-hydroxy-5-chlorophenyl) sulphide) (Cocker Chemical Co.). Fentichlor is an antifungal agent as well as an antibacterial agent which has been in use by dermatologists for many years for the treatment of skin diseases. Recently it has been used in a number of medicated cosmetics and possible applications include foot powders, industrial hygiene creams and medicated soaps.

Fentichlor is claimed to be active in particulate form and is more effective in the acid pH range than under alkaline conditions. Fentichlor suspensions of 2 per cent have been used for the successful treatment of ringworm, favus of the scalp, athlete's foot and barber's rash; although there has been a reasonably good history of dermal tolerance to this antiseptic, Burry[45] has reported cases of photosensitization. Some sources have ascribed this to an impurity, *p*-chlorophenol, which is often present. Further investigation will therefore be necessary before Fentichlor can be recommended for use in mass market products.

Salicylanilides and Carbanilides

Halogenated Salicylanilides. Homologues of both salicylamide and salicylanilide have been used, particularly for their antifungal and antibacterial activity. These materials have been tested and found to be effective as additives in soaps. The compounds mainly concerned are the following:

4′,5-dibromosalicylanilide (DBS)
3′,4′,5-trichlorosalicylanilide (Anobial)
3,4′,5-tribromosalicylanilide (Temasept IV, Tuasal 100, TBS)
2,3,3′-5-tetrachlorosalicylanilide (TCS)
3,3′,4,5′-tetrachlorosalicylanilide (Irgasan BS200, TCS)

Although TBS (Theodore St Just and Co. Ltd) and particularly TCS (Geigy and Co.) (Figure 35.2) have been shown to be highly active germicidal agents both *in vitro* and *in vivo*,[16] one of the factors that have hindered the use of halogenated salicylanilides is the confused literature about their safety. There can now be little doubt that tetrachlorosalicyanilide is potentially dangerous because of its ability to induce photosensitization. Wilkinson,[46] Calnan,[47] Vinson and Flatt,[48] Anderson[49] and Baer[50] have all provided evidence that TCS causes photodermatitis and it is now no longer used in soaps, as the incidence of this kind of reaction is much too high for widespread use.

Although reactions to the polybrominated salicylanilides have been reported (for example dibromosalicylanilide by Behrbohm and Zschunke[51] and tribromosalicylanilide by Epstein,[52] Harber[53] and Osmundsen[54]), these reports require interpretation before manufacturers can decide whether to use these materials or not. Many acceptable antiseptics provoke occasional reactions in hypersensitive individuals, but it is not a question of whether or not positive reations will be obtained if a certain substance is used in a new product, but whether a large number of people will be injured by its use. Complete exclusion of all materials which provoke any form of sensitization is impossible, and testing either on animals or humans with the aim of being absolutely certain is unrealistic since at least 30 000 persons would have to be patch tested before it could be predicted that less than 1 in 10 000 people would be sensitized by the product.

Peck and Vinson[55] have used the Schwartz-Peck and Draize-Shelansky patch tests, modified to include UV irradiation, to test tribromosalicylanilide and dibromosalicylanilide on 150 subjects. No photosensitization was revealed and the authors claim that the result confirms that these materials have a very low photosensitization potential. Moreover, they point out that these germicides have been used in toilet soaps for many years in the USA and that hundreds of millions of bars have been used with excellent consumer acceptance.

A fluorinated derivative, 3,5,dibromo-3′-trifluoromethylsalicylanilide (Fluorophene) (Stecker Chemicals) is claimed to be safer in use than many other germicides of similar potency. It exhibits good light stability, and at 2 per cent in soap does not discolour even after long periods of use. As with the other halogenated salicylanilides, there is likely to be a risk of photosensitization, but no reliable data are available.

Carbanilides. Trichlorocarbanilide (3,4,4′-trichlorocarbanilide) (Monsanto), also known as TCC or Trichlorocarban, is a highly active antibacterial agent which, like Irgasan DP 300, is widely used at concentrations of 1–2 per cent in antibacterial soaps and other toilet preparations. TCC is almost insoluble in water but can be solubilized by certain nonionics. Unlike some of the bisphenols, it does not discolour on exposure to light but, like most phenolic antibacterials, it is more active against Gram-negative than Gram-positive

bacteria. The activity *in vivo* of antibacterial soap bars containing TCC has been investigated by a number of workers (see Table 35.2).

TCC has a reasonably clear record of safety and although isolated cases of photosensitization have been reported there is a fairly general consensus of opinion about its safety for use in shampoos, deodorants, skin products and soaps. Care must be taken, however, to avoid high temperatures in manufacture, since it breaks down to form chloroaniline which is highly toxic.

Another carbanilide, 3-trifluoromethyl-4-4'-dichlorocarbanilide (Irgasan CF3, Anobial TFC) has also been found to have good activity *in vivo* and *in vitro*[12,14,45] (Table 35.2). This compound has not been found to show evidence of photosensitization. Voss[56] showed that *ad lib* use of soaps containing 1·0 per cent TCC and 0·5 per cent Irgasan CF3 over a period of two to seven months reduced the prevalence of *Staph. aureus* on the skin. This study also indicated that partial inhibition of the Gram-positive flora was not accompanied by any increase in Gram-negative species. Ojajarvi[12] showed that an emulsion containing 2 per cent Irgasan CF3 and 0·1 per cent β-phenoxyethanol exerted a sustained antibacterial effect similar to that observed with hexachlorophene preparations, and suggested that this formulation could offer an alternative to hexachlorophene where long-term antisepsis is needed.

Cationic Surface-active Antibacterials

Cationic surface-active antibacterials are widely used in mouthwashes, deodorants, feminine hygiene products, baby products, antidandruff conditioners or rinses, hairdressings and tonics, and astringent lotions. Their antibacterial activity has been widely studied and there has been much confusion in the literature about their comparative effectiveness, mainly because of the different techniques used to evaluate them. Some of the problems which have arisen in testing quaternaries are associated with the bacteriostatic 'carry over' of effective germicides which cannot be eliminated by simple dilution, as in the case of other antiseptics, because quaternaries tend to make bacteria form clumps, and they also adhere strongly to the surface of cells without necessarily killing them. For this reason an effective chemical quenching agent must be added and many workers have failed to do this. In general the quaternaries are more effective against Gram-positive than against Gram-negative bacteria, although the difference is small in the case of some compounds.

It should be noted, however, that Gram-negative organisms, particularly the pseudomonads, are quite frequently found to be resistant to these agents. On a number of occasions *Pseudomonas*, *Enterobacter* and other Gram-negative organisms have been found growing in solutions of benzalkonium chloride, cetrimide and chlorhexidine.[57,58]

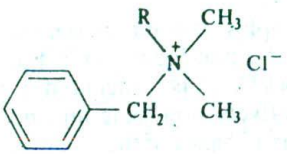
Cationics in general are incompatible with a considerable range of materials, especially anionic compounds (including soaps). These compounds are therefore seldom used in creams and lotions unless nonionic emulsifiers are used, although it should be noted that they may also be inactivated by high concentrations of nonionics (see Chapter 36). Incompatibility with other materials such as silicates, alginates, methylcellulose, lanolin and so on has also been reported.[59–61] The optimum pH range for antimicrobial activity is 7–8 although there is some evidence for greater activity in the alkaline range.[62,63]

Quaternary Ammonium Compounds (QACs). Examples of some of the most widely used of these compounds are given in Table 35.3 and Figure 35.3. From toxicity data summarized by Guklhorn[14] and Block[30], it is concluded that concentrations used for antiseptic purposes are relatively non-toxic and non-irritant when used externally, except to the mucous membranes of the eye where concentrations of 1–2 per cent or above can cause permanent opacity of the cornea.

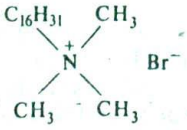
Concentrations of the order of 0·5 per cent QAC are used in hair-rinse products which may come into contact with the eye, and have been found safe. For use on the skin, concentrations of between 0·5 per cent and 1·5 per cent are commonly used, while in mouthwashes, owing to the somewhat bitter taste of most quaternaries, lower concentrations are normally advisable. In deodorants

Table 35.3 Quaternary Ammonium Antibacterial Agents

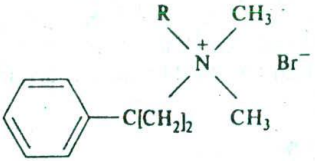
Trade name	Chemical group
Benzalkonium chloride Marinol (Berk) Vantoc CL (ICI) Roccal (Bayer) Zephiran (Bayer) Zephirol (Bayer)	Alkyl-dimethyl-benzyl ammonium chloride
Arquad 16 (Armour Hess)	Alkyl-trimethyl ammonium chloride
Vantoc AL (ICI)	Alkyl-trimethyl ammonium bromide
Cetrimide CTAB Cetavlon (ICI) Morpan CHSA (Glovers)	Cetyl-trimethyl ammonium bromide
Domiphen bromide Bradosol (CIBA)	β-Phenoxyethyl-dimethyl-dodecyl ammonium bromide
Benzethonium chloride Phemerol (Parke Davis) Octaphen (Ward, Blenkinsop) Hyamine 1622 (Rohm and Hass)	*p*-tert-Octylphenoxyethoxyethyl-dimethyl-benzyl ammonium chloride
Fixanol VR (ICI) Vantoc B (ICI)	Tetradecyl-pyridinium bromide
Fixanol C (ICI) Ceepryn (Merrell)	Cetyl-pyridinium bromide or chloride
Diometam (British Hydrological Ltd)	Di-(*n*-octyl)-dimethyl ammonium bromide
Isothan Q (Onyx Chem.)	Alkyl-isoquinolinium bromide



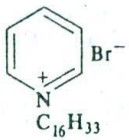
Benzalkonium chloride



Cetavlon

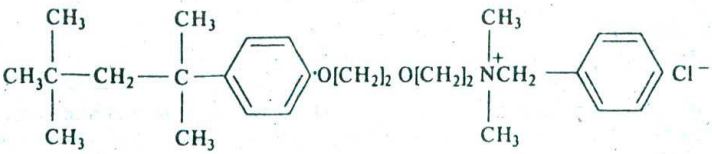


Domiphen

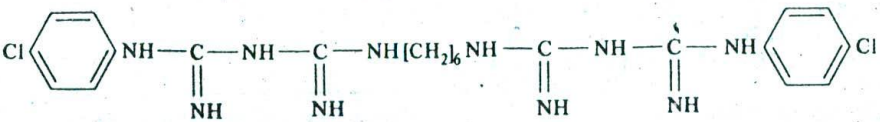


Ceepryn

(R is long-chain alkyl or other group)



Benzethonium chloride



Chlorhexidine

Figure 35.3 Formulae of some cationic surface-active antiseptics

and antiseptic baby powders, levels of 0·1–0·2 per cent are frequent, and rinse products for treating babies' nappies (diapers) usually contain 0·2 per cent at use dilution.

Many of these compounds, notably cetrimide, Domiphen bromide, benzalkonium chloride, Ceepryn, Phemerol and Zephiran, are mentioned in British Pharmacopoeias. Studies of the effectiveness of Zephiran, Ceepryn, cetrimide and other compounds which have been widely used in medical practice for surgical hand disinfection and preparation of skin prior to surgery are summarized by Block.[30]

Since about 1970 there has been an increasing number of hospital reports in which aqueous QACs have been implicated as the source of infection resulting either from intrinsic contamination of the antiseptic solution or its lack of effectiveness against certain pathogens. As a result, the use of these products in medical practice has been seriously questioned by a number of workers.[58,64]

Dowicil 200. 1-(3-Chloroallyl)-3-5-7-triaza-1-azoniaadamantane chloride (Dow Chemicals) is a quaternary ammonium compound which acts by the slow release of formaldehyde in aqueous solution. Dowicil 200 is a broad-spectrum antimicrobial agent but is considered to be rather more effective against bacteria than against fungi and yeasts. Of particular interest is its activity against *Pseudomonas aeruginosa*.

It is highly soluble in water, although solutions discolour on aging and have a characteristic odour. Activity is retained in the presence of both anionic and nonionic detergents and is not markedly affected by pH.

Although the manufacturers report no evidence of primary irritation on human subjects with solutions up to 2 per cent, the possibility of sensitization to breakdown products of this germicide should not be overlooked.

Chlorhexidine. An antiseptic which, although not truly a quaternary compound, nevertheless resembles one in being strongly inhibited by anionic material, has gained prominence in recent years and is probably more effective than most of the true quaternaries. This compound, Hibitane or chlorhexidine (ICI) (1,6,di(N-*p*-chlorophenylguanidino)hexane) (Figure 35.3), which is available as a diacetate and the more soluble digluconate, has good all-round antibacterial properties, very low toxicity and shows no evidence of irritation or sensitization.[65] A number of materials reduce the effectiveness of chlorhexidine, and the presence of free chloride, sulphate, phosphate or carbonate ions causes precipitation. It is also reported to be incompatible with sodium carboxymethyl cellulose, gum tragacanth, alginates, beeswax and formaldehyde. Chlorhexidine salts show optimal activity at pH 6–8.[66]

The activity of aqueous and alcoholic solutions, creams and detergent formulations containing between 0·5 and 4 per cent chlorhexidine used for disinfection of hands and for pre-operative skin disinfection has been extensively investigated.[2–7,12,25,65,67] In general these investigations indicate, as illustrated in Figure 35.1, that chlorhexidine is a rapid-acting antibacterial agent which can be used to produce both immediate reductions in skin flora following a single application and also further reduction after repeated usage.

It should be noted, however, that investigations by Ojajarvi *et al.*[67] indicate that use of 4 per cent chlorhexidine detergent scrub by nursing staff in a neonatal unit for a period of more than a week was associated with increases in skin flora and these workers suggest that more attention should be paid to long-term handwashing tests to assess the efficacy of antiseptics under in-use conditions.

In medical practice, chlorhexidine formulations are widely used as general disinfectants in surgical procedures, in treatment of burns and wounds, and in the prevention of cross-infection. Use of 1 per cent chlorhexidine cream in treatment of wounds and burns is described by Soendergard,[68] Fowler[69,70] and Grant.[71] A combination of 0·05 per cent chlorhexidine and 0·5 per cent

cetrimide is an antiseptic and detergent system that is also used for wound cleansing. In baby powders, 0·1 per cent chlorhexidine hydrochloride confers mild antiseptic properties, while concentrations of less than 0·5 per cent are now used in feminine intimate hygiene products.[72]

The effect of chlorhexidine on the oral flora has also been studied and Löe *et al.*[73,74] have found that a mouthwash containing 0·2 per cent of chlorhexidine digluconate reduces the amount of bacterial plaque which normally forms on the teeth. This had the effect of reducing the formation of calculus and also prevented the onset of gingival inflammation in a panel of students who did not clean their teeth for 3–4 weeks, during which time they rinsed their mouths twice a day with the test mouthwash.

A more extensive review of the properties and clinical usage of chlorhexidine antiseptics is given by Senior[75] and Madsen.[76,77]

Amphoteric Surface-active Compounds

The amphoteric surface-active compounds, or ampholytes, are a group of compounds that combine detergency in their anionic group with bactericidal power in their cationic moiety. The most widely used agents in this group are the Tego compounds which are made up of the amino acid glycine substituted with a long-chain alkyl amine group: $RNH(CH_2CH_2NH)_2CH_2COOH$ where R is an alkyl group, usually C_{10}–C_{16}. Schmitz and Harris[78] showed that the greater the number of nitrogen groups in the surface-active ion, the greater the activity; dodecylglycine is only about one-tenth as active as dodecyl-(aminoethyl)-glycine.

These compounds are claimed to be virucidal and fungicidal as well as bactericidal. One particularly useful property is their surface activity which is associated with good wetting and soil penetrating power.

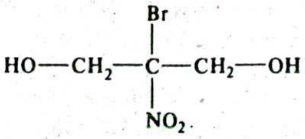
Because these materials are not as susceptible to inactivation by proteins as the quaternary ammonium compounds, they are widely used in industrial products. Their effectiveness is, however, reduced by soaps and other anionic detergents and in some cases by nonionic detergents. The amphoteric bactericides, particularly Tego 103S ($C_{12}H_{25}NH(CH_2)_2NH(CH_2)_2NHCH_2CO_2H.HCl$ as a 15 per cent solution), have been used for skin disinfection and other medical applications.[79]

The toxicity of Tego 103S and other Tego compounds, according to the manufacturer's literature, is very low and there is little or no evidence of skin irritancy or sensitization.

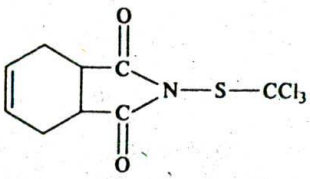
Miscellaneous Antimicrobial Agents

Bronopol (2-Bromo-2-nitropropan-1,3-diol) (The Boots Co.) (Figure 35.4) is a highly water-soluble compound which shows approximately equal activity against Gram-positive and Gram-negative bacteria including *P. aeruginosa*.[80,81] It is also active against fungi at low concentrations and its effectiveness does not vary very much over the pH range 5–8. It is not adversely affected by anionic and nonionic surfactants.[82,83]

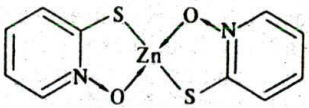
Bronopol does not appear to be a primary irritant at the concentrations normally employed (0·2–0·5 per cent) and tests on guinea-pigs have shown no signs of sensitization. Aqueous solutions of Bronopol gradually decompose under alkaline conditions.



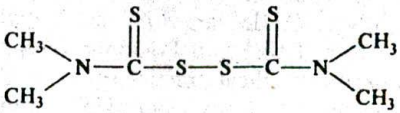
Bronopol



Captan



Zinc pyridine-2-thiol-1-oxide



TMTD

Figure 35.4 Formulae of some miscellaneous antiseptics

Captan. *n*-Trichloromethylthio-4-cyclohexene-1,2-dicarboximide (Figure 35.4) is also known as Vancide 89RE (R.T. Vanderbilt Co.) and is a water-insoluble solid which has been used at 0·1–0·25 per cent in medicated powders. It has also been recommended as an antidandruff agent but there is only scanty evidence of its effectiveness for this purpose. Vancide 89RE is unstable in alkaline conditions but has a reasonably wide spectrum of activity against bacteria and fungi in the acid state. The manufacturers report satisfactory results of tests for corneal damage carried out on aqueous suspensions, and human patch tests have shown no primary irritation after 24 hours application as a 50 per cent aqueous paste.

Dioxin. 6-Acetoxy-2,4-dimethyl-*m*-dioxane (Givaudan) is a clear amber liquid which, when added to water, hydrolyses to produce acetic acid, resulting in a lowering of pH. Dioxin is claimed to be active over a wide pH range. It is particularly effective against Gram-negative bacteria and has been used as a preservative at concentrations between 0·1 per cent and 0·2 per cent. Its main disadvantage is its characteristic odour which is difficult to mask in cosmetic products. Dioxin lotions of 1 per cent cause no irritation or damage to rabbits' eyes and patch tests at this concentration have been carried out on human subjects with satisfactory results.

Germall 115 (Imidazonidyl Urea) (Sutton Laboratories, Inc., Roselle, NJ) is a water-soluble antibacterial which is generally non-toxic and non-irritant and is active against Gram-negative and Gram-positive bacteria and also some yeasts and moulds. It is effective over a wide pH range and retains activity in the presence of proteins and surfactants. The properties of this compound, including toxicity studies, are further discussed by Berke *et al.*[84]

Halogens. Although iodine solutions, as such, are now little used because of their irritant and skin staining properties, they have largely been replaced by the iodophors. Iodophors are mixtures of iodine with surface-active agents which are used as antiseptics at concentrations between about 0·5 and 1 per cent available iodine. They have a low vapour pressure and almost complete lack of odour, low irritant properties,[85] and are non-staining. They are active against Gram-negative and Gram-positive bacteria and also have fungicidal, sporicidal and virucidal activity. Optimum activity is observed in acid solution (pH 3–4).

Iodophors may be formulated with anionic, cationic and nonionic surface-active agents and the resulting solubilized products have the added advantage that the system acts as a skin cleanser as well as an antiseptic. Some commercial products are made with compounds such as polyvinylpyrrolidone and polyethoxyethanol derivatives. Trade names include Betadine (Berk), Wescodyne (Bebgue), Virac (Ruson Labs) and Povidone-Iodine (Berk).

Iodophors are widely used in medical practice for skin-degerming by hospital personnel and for pre-operative and post-operative skin disinfection and antisepsis. The activity of iodophors compared with chlorhexidine and other skin disinfectants has been investigated by a number of workers.[3–6,12,86] These investigations indicate that iodophors, like chlorhexidine formulations, have the advantage of producing good immediate effects after a single application with further reductions in skin flora after repeated or prolonged usage.

Other pharmaceutical/cosmetic iodophor formulations that are available include shampoos, mouthwashes, and skin and scalp cleansers.

Sodium hypochlorite and the various organic chlorine-releasing compounds such as Chloramine T are also highly active bactericidal, fungicidal and virucidal agents and are used extensively as general disinfectants in public health and the domestic environment. Although used widely for disinfection of wounds in hospitals they are not generally employed as skin disinfectants, probably because of their unpleasant smell and their tendency to produce skin irritation at concentrations of more than about 0·5 per cent available chlorine.

Mercury Compounds. Inorganic mercury compounds such as mercuric chloride and mercuric nitrate are still used in medical practice for skin disinfection but are scarcely used at all in toilet preparations. Organic compounds such as phenylmercuric nitrate, borate and acetate are used in shaving creams and antidandruff lotions in the United Kingdom although their use is restricted by the Poisons Rules 1978 in which a third schedule entry (exempted from provisions of Poisons Rules provided that a prescribed limit is not exceeded) applies to toilet, cosmetic and therapeutic preparations containing not more than 0·01 per cent of phenylmercuric salts. The toxic effects of mercury compounds are further considered in Chapter 36. Compounds of mercury are highly active against both

Gram-negative and Gram-positive organisms but, despite their excellent antibacterial properties, their use in products for mass-market sale is difficult to justify.

Pyridine N-oxides. The pyridine N-oxides, also known as cyclic thiohydroxamic acids or pyridinethiones, are highly active antibacterial and antifungal agents. Cox[87] has described their preparation and properties and reviewed their application as antibacterials and fungicides, while Snyder *et al.*[88] have reviewed the safety aspects. Snyder states that of some 1350 compounds screened in his laboratory, one of the most active antifungal and antibacterial materials examined was zinc pyridine-2-thiol-1-oxide (ZnPTO) (Figure 35.4), also known by the trade name Omadine (Olin Mathieson Chemicals).

Brauer *et al.*[89] claim that the compound is several hundred times more effective against *Staphylococcus aureus*, *S. albus* and *Pityrosporum ovale* than many of the traditional materials used in antidandruff treatments. Shampoos containing 2 per cent of ZnPTO appear to be extremely effective against dandruff and are on sale in the USA, the UK and Europe. A men's hair dressing containing 0·5 per cent of ZnPTO has also been shown by Brauer *et al.*[89] to be effective against dandruff.

Cadmium, titanium and zirconium pyridinethiones have also been prepared and found to be effective antimicrobial agents.

Tenenbaum *et al.*[90] have compared the antimicrobial properties of many agents used in antidandruff treatments and have concluded that, although ZnPTO is an exceptionally potent antimicrobial agent, it must owe its dramatic effects against dandruff to a property other than its antimicrobial activity, since other antiseptics which were more potent *in vitro* were significantly less effective against dandruff in clinical trials.

Snyder *et al.*[88] found rodents to be particularly susceptible to oral ingestion of low concentrations, which produced paralytic symptoms. In tests on dogs, they found no effects attributable to a shampoo formulation containing 2 per cent, but dogs were the most susceptible species to the effects of the compound itself, and after oral administration as a water-in-oil emulsion at a level of 2·5 mg per kg, ocular manifestations were observed. However, the same dose had no ocular or other toxic effects when given to monkeys.

Opdyke *et al.*[91] claim that, in their experience over a period of eight years, ZnPTO does not penetrate the skin and does not produce toxic reactions when used with normal precautions. Collom *et al.*[92] and Coulston *et al.*,[93] however, demonstrated partial absorption of zinc and sodium omadine through the skin of rats, rabbits and monkeys.

In using these compounds in toilet preparations it is therefore important that possible toxic hazards to process workers and consumers are carefully considered.

Tetramethylthiuram Disulphide. TMTD (3,4,5-tetramethylthiuram disulphide) (Figure 35.4) is an antibacterial agent which has also been used in antibacterial soaps. Handwashing tests indicate that 1 per cent TMTD in soap produces 76 per cent reduction in count of skin bacteria over seven days (Table 35.2).

Although insoluble in water, TMTD has high activity against Gram-positive organisms, while its effect against Gram-negatives is higher than many of the other compounds previously mentioned. Drawbacks to its use in cosmetic products are its tendency to discolour and its lack of stability, which leads to liberation of thio odours. The compound is also known to produce irritant effects although it is recognized that this may be due to an oxidation product.

Synergism

The use of synergistic combinations of antimicrobial agents both for preservation and antiseptic purposes is widely reported in the literature. The term 'synergism' used here refers to an antibacterial effect greater than the sum of the antibacterial effects of the separate components.

Noel *et al.*[94] describes the enhancement of antibacterial activity by combining halogenated bisphenols with halogenated aromatic anilides or with halogenated carbanilides. Synergistic effects were specifically demonstrated for 3,4,4'-trichlorocarbanilide and 3,3',4-trichlorocarbanilide with hexachlorophene, the sulphur analogue of hexachlorophene, tetrachlorophene, bithionol and 2,2'-thio*bis*-(4-chloro,6-methylphenol). Other synergistic combinations comprised 2-hydroxy-5-chlorobenzoic acid, 3',4'-dichloroanilide and 2-hydroxy-5-chlorobenzoic acid, 3'4"-dichloroanilide and 2-hydroxy-5-chlorobenzoic acid 4'-chloroanilide in mixtures with hexachlorophene and the sulphur anologue of hexachlorophene (bithionol) and tetrachlorophene. These synergistic pairs of antiseptics are covered by US and other patents.[95]

Several other examples of synergistic combinations are given by Casely *et al.*[96] who have shown the ability of various substituted ureas, other than the well-known trichlorocarbanilides, to form combinations with synergistic activity with hexachlorophene. Moore and Hardwick[97] demonstrated synergistic effects of certain ampholytes with cetrimide, while Barr *et al.*[98] have shown that organic mercury compounds can be used to potentiate the activity of bisphenols. Further examples of synergism given in Chapter 36 refer mainly to compounds used as preservatives.

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