

SECOND EDITION

Pharmaceutics

THE SCIENCE OF
DOSAGE FORM DESIGN

Edited by
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Where maximum stability dictates wider values, it is important for injections that there is low buffer capacity to prevent unnecessary challenge to the homeostatic pH (7.4) of blood.

Weakly acidic and basic drugs are most soluble when ionized, and it is then that instability is most likely as they are charged. This leads to a problem, as many potent drugs are extremely poorly soluble and pH ionization is the most obvious method to obtain a solution. In some cases, therefore, the inclusion of a water-miscible solvent in the formulation will increase stability by:

1. Suppressing ionization
2. Reducing the extreme of pH required to achieve solubility
3. Reducing water activity by reducing the polarity of the solvent, e.g. 20% propylene glycol in chlordiazepoxide HCl injection.

Reactions in aqueous solution are usually catalysed by pH, and this is monitored by measuring degradation rates (usually pseudo first order) against pH, keeping temperature, ionic strength and solvent concentration constant. Suitable buffers include acetate, citrate, lactate, phosphate and ascorbate (an intrinsic antioxidant).

Solvolysis

Where the reacting solvent is not water, then breakdown is termed solvolysis. Furthermore, the definition can be extended to include any change in solvent polarity (usually measured as dielectric constant) as a result of increased ionic strength. Phenobarbitone is considerably more stable in preparations containing water-miscible solvents, whereas aspirin, which undergoes extensive hydrolysis, is degraded further by aqueous solvents. Both effects are directly related to the dielectric constant (polarity) of the solvent. In general, if a compound produces degradation products which are more polar than the addition of a less polar solvent will stabilize the formulation. If the degradation products are less polar, then the vehicle should be more polar to improve stability. With the hydrolysis of neutral non-polar drugs, e.g. steroids, the transition state will be non-polar with no net charge. In this case solvents will not affect the rate of decomposition and can be used with impunity to increase solubility.

Oxidation

Oxidation is controlled by the environment, i.e. light, trace metals, oxygen and oxidizing agents. Reduction

is a complimentary reaction (redox) and there is a mutual exchange of electrons. Oxidation is a loss of electrons and an oxidizing agent must be able to take electrons. In organic chemistry, oxidation is synonymous with dehydrogenation (the loss of hydrogen) and this is the mode of action of polyhydroxyphenol antioxidants, e.g. hydroquinone. However, most antioxidants function by providing electrons or labile H^+ , which will be accepted by any free radical to terminate the chain reaction. A prerequisite for effective antioxidant activity in any particular preparation is that the antioxidant is more readily oxidized than the drug.

Chelating agents

Chelating agents are complexes, unlike simple ligands, e.g. ferrocyanide ($Fe(CN)_6^{4-}$), which form complex salts by a single bond provided by a lone electron pair. Chelating agents are capable of forming more than one bond. For example, ethylene diamine is bidentate (two links), tripyridyl is tridentate (three) and ethylene diamine tetra-acetic acid (EDTA) is hexadentate (six), which makes it particularly effective as a pharmaceutical chelating agent.

Photolysis

Oxidation, and to some extent hydrolysis, is often catalysed by light. The energy associated with this radiation increases as wavelength decreases, so that the energy of UV visible is greater than that of IR and is independent of temperature (Table 8.12).

When molecules are exposed to electromagnetic radiation they absorb light (photons) at characteristic wavelengths which causes an increase in energy, which can:

- cause decomposition
- be retained or transferred
- be converted to heat
- result in light emission at a new wavelength (fluorescence, phosphorescence).

Type of radiation	Wavelength (nm)	Energy (kcal mol ⁻¹)
UV	50-400	287-72
Visible	400-750	72-36
IR	750-10 000	36-1

Miscellaneous solvents

Isopropyl myristate and isopropyl palmitate are used as solvents for external use, particularly in cosmetics, where their low viscosity and lack of greasiness make them pleasant to use. Dimethylformamide and dimethylacetamide have both been used as solvents in veterinary formulation, but their toxicities render them unsuitable for human use. Kerosene too is also limited in its application, being used mainly as a solvent for insecticides such as pyrethrum and piperonyl butoxide.

Xylene is present in some ear drops for human use to dissolve ear wax, and glycofurol is a useful solvent for parenteral products.

As with aqueous systems, it may be possible to improve the solubility of a drug in a particular vehicle by the addition of a cosolvent. For example, nitrocellulose is poorly soluble in both alcohol and ether but adequately soluble in a mixture of both. The formulation of Digoxin Injection, too, is best achieved by the inclusion of both ethyl alcohol and propylene glycol.

OTHER FORMULATION ADDITIVES

Buffers

These are materials which, when dissolved in a solvent, will enable the solution to resist any change in pH should an acid or an alkali be added. The choice of suitable buffer depends on the pH and buffering capacity required. It must be compatible with other excipients and have a low toxicity. Most pharmaceutically acceptable buffering systems are based on carbonates, citrates, gluconates, lactates, phosphates or tartrates. Borates can be used for external application, but not to mucous membranes or to abraded skin.

Although solutions of drugs that are themselves weak electrolytes will act as buffers, their buffering capacities are not usually sufficiently robust and should be enhanced by one of the systems described above.

As the pH of most body fluids is 7.4, products such as injections, eye drops and nasal drops should, in theory, be buffered at this value to avoid irritation. Many body fluids themselves, however, have a buffering capacity and, when formulating low-volume intravenous injections or eye drops, a wider pH range can be tolerated. This is potentially useful should a compromise be necessary when choosing a pH that is physiologically acceptable for a drug whose optimum stability, solubility and/or bioavail-

ability may depend on different pHs. For further details on the use of buffers see Chapters 3 and 35.

Density modifiers

It is rarely necessary to control the density of solutions except when formulating spinal anaesthetics. Solutions of lower density than cerebrospinal fluid will tend to rise after injection and those of higher density will fall. Careful control both of the density of such injections and of the position of the patient on the operating table will enable precise control of the area to be anaesthetized. The terms used to describe the density of injections in relation to that of spinal fluid are isobaric, hypobaric and hyperbaric, meaning of equal, lower and higher density, respectively. The most widely used material for density modification is dextrose.

Isotonicity modifiers

Solutions for injection, for application to mucous membranes, and large-volume solutions for ophthalmic use must be made iso-osmotic with tissue fluid to avoid pain and irritation.

The most widely used isotonicity modifiers are dextrose and sodium chloride. Isotonicity adjustments can only be made after the addition of all other ingredients, because each ingredient will contribute to the overall osmotic pressure of a solution.

Viscosity enhancement

It may be difficult for aqueous-based topical solutions to remain in place on the skin or in the eyes for any significant time because of their low viscosities. To counteract this effect, low concentrations of gelling agents can be used to increase the apparent viscosity of the product. Examples include povidone, hydroxyethylcellulose and carbomer.

Preservatives

When choosing a suitable preservative it must be ensured that:

- adsorption of the preservative onto the container from the product does not occur, and
- its efficiency is not impaired by the pH of the solution or by interactions with other ingredients.

For example, many of the widely used parahydroxybenzoic acid esters can be adsorbed into the micelles of some non-ionic surfactants and, although their presence can be detected by chemical analysis, they are in fact unable to exert their

antimicrobial activities. It is only by full microbiological challenge testing that the efficiency of a preservative system can be properly assessed.

A more comprehensive discussion on the preservation of pharmaceuticals can be found in Chapter 42.

Reducing agents and antioxidants

The decomposition of pharmaceutical products by oxidation can be controlled by the addition of reducing agents such as sodium metabisulphite, or antioxidants such as butylated hydroxyanisole or butylated hydroxytoluene. For unit-dose parenteral products, such as injections of nicotinamide and ascorbic acid, it is possible to use Water for Injections free from dissolved air and to replace the air in the headspace by nitrogen or another inert gas.

Sweetening agents

Low molecular weight carbohydrates, and in particular sucrose, are traditionally the most widely used sweetening agents. Sucrose has the advantages of being colourless, very soluble in water, stable over a pH range of about 4–8 and, by increasing the viscosity of fluid preparations, will impart to them a pleasant texture in the mouth. It will mask the taste of both oily and bitter drugs and has a soothing effect on the membranes of the throat. For this reason, despite its fermentable properties, sucrose is particularly useful as a vehicle for mucous preparations.

Polysaccharide alcohols such as sorbitol, mannitol and, to a lesser extent, glycerol, also possess sweetening power and can be included in preparations for diabetic use, where sucrose is undesirable. Other less widely used bulk sweeteners include maltitol, isosorbide, sorbitol, fructose and xylitol. Treacle, honey and liquorice are now very rarely used, having only a minor application in some extemporaneously prepared formulations.

Artificial sweeteners can be used in conjunction with sugars and alcohols to enhance the degree of sweetness, or on their own in formulations for patients who must restrict their sugar intake. They are also termed intense sweeteners because, weight for weight, they are hundreds and even thousands of times sweeter than sucrose and are therefore rarely required at a concentration greater than about 0.2%.

Only about six artificial sweeteners are permitted for oral use within the European Union, the most widely used being the sodium or calcium salts of saccharin (E954). Both exhibit high water solubility and are chemically and physically stable over a wide pH

range. Less widely used are aspartame (E951), which is a compound of L-aspartic acid and L-phenylalanine, acesulfame potassium (E950), thaumatin (E957), sodium cyclamate (E952) and neohesperidine DC (E959). The main disadvantage of all artificial sweeteners is their tendency to impart a bitter or metallic aftertaste, and they are therefore often formulated with sugars to mask this.

Flavours and perfumes

The simple use of sweetening agents may not be sufficient to render palatable a product containing a drug with a particularly unpleasant taste. In many cases, therefore, a flavouring agent can be included. This is particularly useful in paediatric formulation to ensure patient compliance. The inclusion of flavours has the additional advantage of enabling the easy identification of liquid products.

Flavouring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon, herbs and spices, and distilled fractions of these. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or essences, and are particularly widely used in the manufacture of products for extemporaneous use. Artificial perfumes and flavours are of purely synthetic origin, often having no natural counterpart. They tend to be cheaper, more readily available, less variable in chemical composition and more stable than natural products. They are usually available as alcoholic or aqueous solutions or as powders.

The choice of a suitable flavour can only be made as a result of subjective assessment and, as consumer preferences vary considerably, this is not easy. Some guidance can, however, be given by reference to Table 21.1, which shows that certain flavours are particularly useful for the masking of one or more of the basic taste sensations of saltiness, bitterness, sweetness and sourness. These tastes are detected by sensory receptors on various areas of the tongue,

Taste of product	Suitable masking flavour
Salty	Apricot, butterscotch, liquorice, peach, vanilla
Bitter	Anise, chocolate, mint, passion fruit, wild cherry
Sweet	Vanilla, raisins, berries
Sour	Citrus fruits, liquorice, raspberry

whereas the more subtle flavours are detected by the olfactory receptors.

In many cases there is a strong association between the use of a product and its flavour or perfume content. For example, products intended for the relief of indigestion are often mint flavoured. This is because for many years mint has been used in such products for its carminative effect, but even in products containing other active agents the odour and taste of mint are now firmly associated with antacid activity. Similarly, the odour of terpineol is often associated with antiseptic activity and, in a competitive market, it may therefore be unwise to alter these flavours or perfumes to any appreciable extent.

The fact that personal preferences for flavours and perfumes often vary with age can also aid the formulator. Children, in general, prefer fruity tastes and smells, whereas adults choose flowery odours and acid flavours. Other suitable materials for the masking of unpleasant tastes include menthol, peppermint oil and chloroform. In addition to having their own particular tastes and odours they also act as desensitizing agents by exerting a mild anaesthetic effect on the sensory taste receptors.

Flavour-enhancing agents such as citric acid for citrus fruits and glycine or monosodium glutamate for general use are now becoming more widely used.

Colours

Once a suitable flavour has been chosen, it is often useful to include a colour associated with that flavour in order to improve the attractiveness of the product. Another reason for the inclusion of colours is to enable easy product identification, particularly of poisonous materials, including weedkillers and mineralized methylated spirit, and, for example, to differentiate between the many types of antiseptic solution used in hospitals for the disinfection of skin, instruments, syringes etc.

The presence of a strongly coloured degradation product, which does not affect the use of the product, may occasionally be masked by the use of a suitable colour. It is however, essential to ensure that any colour chosen is acceptable in the country in which the product is to be sold. A colour that is acceptable in one country may not be acceptable in another, and as aspects of colour legislation can change quite frequently it is necessary to ensure that only the latest regulations are consulted. The legal departments of most dye manufacturers are usually willing to supply up-to-date information.

The proliferation of nomenclature that exists for most colours can also cause confusion. For example,

the water-soluble dye amaranth is also known as Bordeaux S, CI Food Red 9 and CI Acid Red 27. It has been allocated the Colour Index Number 16185 by the Society of Dyers and Colourists and the American Association of Textile Chemists and Colorists. Under the USA Food, Drug and Cosmetics Act it is known as FD and C Red Number 2, and a directive of the Council of European Communities has allocated it the reference number E 123.

As with flavours and perfumes, there is a range of both natural and synthetic colours. The former, which tend to be more widely acceptable, can be classified into carotenoids, chlorophyll, anthocyanins, and a miscellaneous group which includes riboflavines, caramel and extracts of beetroot. They can, however, exhibit the usual problems associated with natural products, namely variations in availability and chemical composition, both of which may cause formulation difficulties.

Synthetic or 'coal tar' dyes tend to give bright colours and are generally more stable than natural materials. Most of those that are suitable for pharmaceutical use are the sodium salts of sulphonic acids, and therefore they may be incompatible with cationic drugs. Care must also be taken to ensure that any dye used is not adversely affected by pH or by ultraviolet radiation, or by the inclusion of oxidizing or reducing agents or surfactants.

TYPES OF PREPARATION

The terminology used for the titles of different forms of liquid preparation for both oral and topical use can sometimes be confusing, with overlap between definitions and more than one definition being appropriate for one particular product. Furthermore, definitions can vary between different official compendia and may be at variance with definitions used within the pharmaceutical industry. This section attempts to give an overview of the types of pharmaceutical solution available.

Liquids for cutaneous application

Lotions, liniments, paints and collodions

Lotions can be formulated as solutions, and are designed to be applied to the skin without friction. They may contain humectants, so that moisture is retained on the skin after application of the product, or alcohol, which evaporates quickly, imparting a cooling effect and leaving the skin dry.

Mineral oil-based clays (such as bentonite and aluminum magnesium silicate) and colloidal silicon dioxide are used mainly for external use. Aluminium and magnesium hydroxides are also used internally. For example, Liquid Paraffin and Magnesium Hydroxide Oral Emulsion BP is stabilized by the incorporation of the magnesium hydroxide.

Other formulation additives

Buffers

The inclusion of buffers (see Chapters 3, 21 and 35) may be necessary to maintain chemical stability, control toxicity or ensure physiological compatibility. It must be remembered, however, that the addition of electrolytes may have profound effects on the physical stability of suspensions and emulsions.

Density modifiers

From a qualitative examination of Stokes' law (Chapter 6) it can be seen that if the disperse and continuous phases both have the same densities then sedimentation or creaming will not occur. Minor modifications to the aqueous phase of a suspension or emulsion by incorporating sucrose, dextrose, glycerol or propylene glycol can be achieved, but because of the differing coefficients of expansion this can only be possible over a small temperature range.

Humectants

Glycerol, polyethylene glycol and propylene glycol are examples of suitable humectants that can be incorporated at concentrations of about 5% into aqueous suspensions for external application. They are used to prevent the product from drying out after application to the skin.

They can also be added to an emulsion formulation in order to reduce the evaporation of the water, either from the packaged product when the closure is removed or from the surface of the skin after application. High concentrations, if used topically, may actually remove moisture from the skin, thereby dehydrating it.

Antioxidants

Before including an antioxidant in emulsion formulations, it is essential to ensure that its use is not restricted in whichever country it is desired to sell the product. In Britain, butylated hydroxyanisole (BHA) is widely used for the protection of fixed oils and fats at concentrations of up to 0.02% and for some essential oils up to 0.1%. A similar antioxidant

is butylated hydroxytoluene (BHT), which is recommended as an alternative to tocopherol at a concentration of 10 ppm to stabilize liquid paraffin. Other antioxidants widely used for emulsion formulation include the propyl, octyl and dodecyl esters of gallic acid, recommended for use at concentrations up to 0.001% for fixed oils and fats and up to 0.1% for essential oils.

The efficiency of an antioxidant in a product will depend on many factors, including its compatibility with other ingredients, its oil/water partition coefficient, the extent of its solubilization within micelles of the emulgent, and its sorption on to the container and its closure. It must be realized, therefore, that the choice of antioxidant and the concentration at which it is to be used can only be determined by testing its effectiveness in the final product and in the package in which the product is to be sold.

Flavours, colours and perfumes

The use of these ingredients is discussed in Chapter 21 and the information there will be directly applicable to suspension and emulsion formulation.

Adsorption of these materials on to the surfaces of the dispersed phase of a suspension may occur, and because of the high surface area of the dispersed powders in this type of formulation, their effective concentrations in solution may be significantly reduced. The finer the degree of subdivision of the disperse phase, the paler may appear the colour of the product for a given concentration of dye.

It must also be realized that the inclusion of these adjuvants may alter the physical characteristics of both suspensions and emulsions. Either the presence of electrolytes or their effect on pH can influence the degree of flocculation.

Sweetening agents

Suitable sweeteners are discussed in Chapter 21. High concentrations of sucrose, sorbitol or glycerol, which will exhibit Newtonian properties, may adversely affect the rheological properties of the suspension. Synthetic sweeteners may be salts and can affect the degree of flocculation.

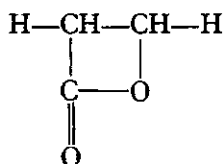
Preservation of suspensions and emulsions

Preservation of suspensions

The section covering the preservation of emulsions is applicable also to suspension formulation. It is

agent and an alkylating agent, reacting with carbonyl, thiol and hydroxyl groups. In order to be effective the gas must dissolve in a film of moisture surrounding the bacteria, and for this reason relative humidities in the order of 75% are required. Formaldehyde used in conjunction with low-temperature steam is a very effective sterilization medium.

β -Propiolactone



This is a colourless liquid at room temperature, with a pungent odour and a boiling point of 162°C. It has a wide spectrum of activity, the vapour being bactericidal to both Gram-positive and Gram-negative bacteria, viruses, rickettsiae, fungi and also *Mycobacterium* species. It is less active against bacterial spores. It is faster acting than formaldehyde and does not give problems with polymerization, but it has feeble penetrating powers. In order to sterilize enclosed spaces concentrations between 2 and 5 mg L⁻¹ of air are necessary at a relative humidity of 80%, and these conditions must be maintained for 2 hours at 24°C.

Unfortunately, the use of β -propiolactone has been limited by doubts about its safety, as there is evidence showing it to be carcinogenic in animals. Acute short-term inhalation exposure causes severe irritation of the eyes, nose, throat and respiratory tract. Acute dermal exposure may cause irritation of the skin, blistering or burns. It has been used in liquid form for the sterilization of rabies vaccine and of various graft tissues.

Propylene oxide

Propylene oxide is a liquid (boiling point = 34°C) at room temperature which requires heating to volatilize. It is inflammable between 2.1 and 21.5% by volume in air, but this can be reduced by mixing with CO₂. Its mechanism of action is similar to that of ethylene oxide and involves the esterification of carbonyl, hydroxyl, amino and sulphydryl groups present on protein molecules. It is, however, less effective than ethylene oxide in terms of its antimicrobial activity and its ability to penetrate materials. Whereas ethylene oxide breaks down to give ethylene glycol or ethylene chlorohydrin, both of which are toxic, propylene oxide breaks down to propylene glycol, which is much less so.

Methyl bromide

Methyl bromide boils at 3.46°C and is a gas at room temperature. It is used as a disinfectant and a fumigant at concentrations of 3.5 mg L⁻¹ with a relative humidity between 30 and 60%. It has inferior antimicrobial properties compared to the previous compounds but has good penetrating power.

Gas plasmas

A plasma is formed by applying energy to a gas or vapour under vacuum. Natural examples are lightning and sunlight, but plasmas can also be generated under low energy such as in fluorescent strip lights. Within a plasma, positive and negative ions, electrons and neutral molecules collide to produce free radicals. The destructive power of these entities has already been described, and so plasmas can be used as biocidal agents in a variety of applications. This type of system can be produced at temperatures below 50°C using vapours generated from hydrogen peroxide or peracetic acid.

ANTIMICROBIAL EFFECTS OF CHEMICAL AGENTS

Chemical agents have been used since very early times to combat such effects of microbial proliferation as spoilage of foods and materials, infection of wounds and decay of bodies. Thus, long before the role of microorganisms in disease and decay was recognized salt and sugar were used in food preservation, a variety of oils and resins were applied to wounds and employed for embalming, and sulphur was burned to fumigate sick rooms.

The classic researches of Pasteur, which established microorganisms as causative agents of disease and spoilage, paved the way for the development and rational use of chemical agents in their control. Traditionally, two definitions have been established describing the antimicrobial use of chemical agents. Those used to destroy microorganisms on inanimate objects are described as **disinfectants**, and those used to treat living tissues, as in wound irrigation, cleansing of burns or eye washes, are called **antiseptics**. Other definitions have been introduced to give more precise limits of meaning, namely, **bactericide** and **fungicide** for chemical agents that kill bacteria and fungi, respectively; and **bacteriostat** and **fungistat** for those that prevent the growth of a bacterial or fungal population. The validity of drawing a rigid demarcation line between those compounds that

kill and those that inhibit growth without killing is doubtful. In many instances concentration and time of contact are the critical factors. The term **preservative** describes those antimicrobial agents used to protect medicines, pharmaceutical formulations, cosmetics, foods and general materials against microbial spoilage, and **biocide** is a general term for antimicrobial chemicals, but it excludes antibiotics and other agents used for systemic treatment of infections.

The mechanisms whereby biocides exert their effects have been intensively investigated and the principal sites of their attack upon microbial cells identified. These are the cell wall, the cytoplasmic membrane and the cytoplasm. Chemical agents may weaken the cell wall, thereby allowing the extrusion of cell contents, distortion of cell shape, filament formation or complete lysis. The cytoplasmic membrane, controlling as it does permeability, and being a site of vital enzyme activity, is vulnerable to a wide range of substances that interfere with reactive groups or can disrupt its phospholipid layers. Chemical and electrical gradients exist across the cell membrane and these represent a proton-motive force which drives such essential processes as oxidative phosphorylation, adenosine triphosphate (ATP) synthesis and active transport; several agents act by reducing the proton-motive force. The cytoplasm, site of genetic control and protein synthesis, presents a target for those chemical agents that disrupt ribosomes, react with nucleic acids or generally coagulate protoplasm.

Principal factors affecting activity

The factors most easily quantified are temperature and concentration. In general an increase in temperature increases the rate of kill for a given concentration of agent and inoculum size. The commonly used nomenclature is Q_{10} (temperature coefficient), which is the change in activity of the agent per 10°C rise in temperature (e.g. Q_{10} phenol = 4).

The effect of change in concentration of a chemical agent upon the rate of kill can be expressed as:

$$\eta = \frac{\log t_2 - \log t_1}{\log C_1 - \log C_2}$$

where C_1 and C_2 represent the concentrations of agent required to kill a standard inoculum in times t_1 and t_2 . The concentration exponent η represents the slope of the line when log death time (t) is plotted against log concentration (C).

When values of η are greater than 1, changes of concentration will have a pronounced effect. Thus, in the case of phenol, when $\eta = 6$, halving the concentration will decrease its activity by a factor of 2⁶

(64-fold), whereas for a mercurial compound, $\eta = 1$, the same dilution would only reduce activity twofold (2¹). Further details and tabulations of both temperature coefficients and concentration exponents may be found in Denyer and Wallhaeusser (1990).

The range of chemical agents

The broad categories of antibacterial chemical compounds have remained surprisingly constant over the years, with phenolics and hypochlorites comprising the major disinfectants and quaternary ammonium compounds widely used as antiseptics. The compounds capable of use as preservatives in preparations for oral, parenteral or ophthalmic administration are obviously strictly limited by toxicity requirements. As concerns over toxicity have intensified the range of available preservatives has diminished: mercury-containing compounds, for example, are now very little used for the preservation of parenteral and ophthalmic products, and the high cost of research and testing coupled with the poor prospects for an adequate financial return militate against the introduction of new agents. For this reason there is a tendency towards the use of existing preservatives in combination, with a view to achieving one or more of the following benefits: synergy; a broader antimicrobial spectrum; or reduced human toxicity resulting from the use of lower concentrations. The subjects of preservative toxicity and their potentiation and synergy are reviewed by Denyer and Wallhaeusser (1990), and Hugo and Russell (1999) have described in detail characteristics of the commonly used biocides.

Phenolics

Various phenolic compounds are shown in Figure 41.4.

Various distillation fractions of coal tar yield phenolic compounds, including cresols, xylenols and phenol itself, all of which are toxic and caustic to skin and tissues. Disinfectant formulations traditionally described as 'black fluids' and 'white fluids' are prepared from higher-boiling coal tar fractions. The former make use of soaps to solubilize the tar fractions in the form of stable homogenous solutions, whereas the latter are emulsions of the tar products and unstable on dilution.

Remarkable success has been achieved in modifying the phenol molecule by the introduction of chlorine and methyl groups, as in chlorocresol and chloroxylenol. This has the dual effect of eliminating toxic and corrosive properties while at the same time enhancing and prolonging antimicrobial activity.

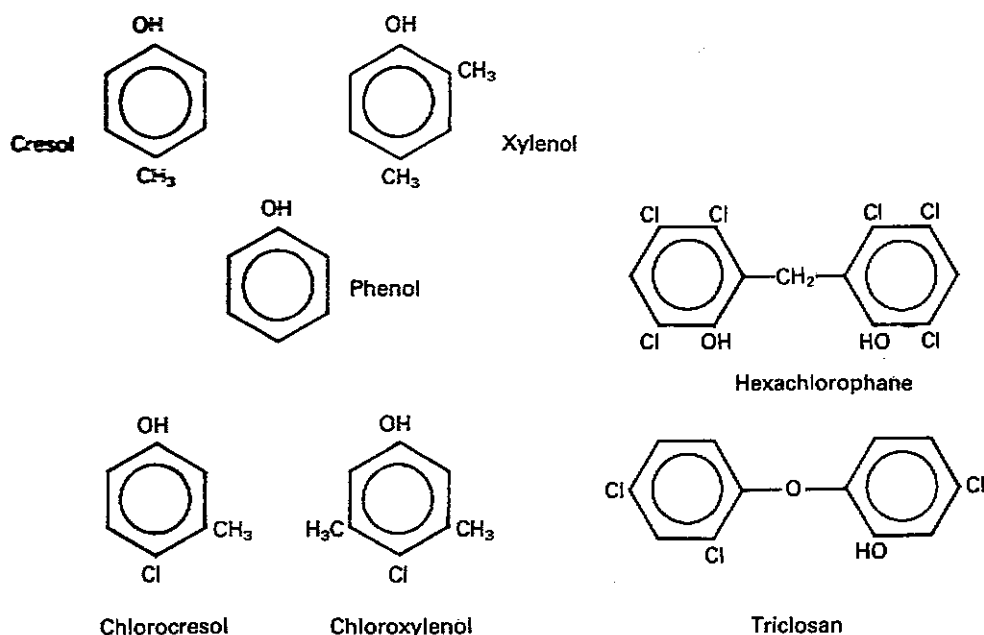


Fig. 41.4 Chemical structures of a range of phenols.

Thus, chlorocresol is used as a bactericide in injections and to preserve oil-in-water creams, whereas chloroxylenol is employed as a household and hospital antiseptic. Phenol may itself be rendered less caustic by dilution to 1% w/v or less for lotions and gargles, or by dissolving in glycerol for use as ear drops. Bisphenols, such as hexachlorophane and triclosan (Irgasan), share the low solubility and enhanced activity of the other phenol derivatives described, but have a substantive effect which makes them particularly useful as skin antiseptics. Formulated as creams, cleansing lotions or soaps, they have proved valuable in reducing postoperative and cross-infection. Again toxicity concerns have emerged, and so, for example, hexachlorophane is restricted in the UK both in respect of the concentrations that may be employed and the type of product in which it may be used.

Phenols generally are active against vegetative bacteria and fungi, are readily inactivated by dilution and organic matter, and are most effective in acid conditions. Depending on concentration, phenols may cause cell lysis at low concentrations, or general coagulation of cell contents at higher concentrations.

Alcohols, aldehydes, acids and esters

Ethyl alcohol has long been used, usually as 'surgical spirit' for rapid cleansing of preoperative areas of

skin before injection, and is most effective at concentrations of 60–70%. It is rapidly lethal to bacterial vegetative cells and fungi, but has no activity against bacterial endospores and little effect on viruses. The effect of aromatic substitution is to produce a range of compounds which are less volatile and less rapidly active and find general use as preservatives, e.g. phenylethanol for eye drops and contact lens solutions, benzyl alcohol in injections, Bronopol (2-bromo-2-nitropropane-1,3-diol) in shampoos and other toiletries. Phenoxylethanol, which has good activity against *Ps. aeruginosa*, has been used as an antiseptic. In general the alcohols act by disrupting the bacterial cytoplasmic membrane and can also interfere with the functioning of specific enzyme systems contained within the membrane.

Formaldehyde and glutaraldehyde are both powerful disinfectants, denaturing protein and destroying vegetative cells and spores. Formaldehyde is used in sterilization procedures both as a gas and as a solution in ethyl alcohol. Glutaraldehyde solutions are also used to sterilize surgical instruments.

The organic acids, sorbic and benzoic and their esters, because of their low toxicity, are well established as preservatives for food products and medicines (see Chapter 42). The exact mode of action of these agents on microorganisms is still uncertain, but they have been shown to influence the pH gradient

across the cell membrane, and at higher concentrations the parabens induce leakage of intracellular constituents.

Quaternary ammonium compounds

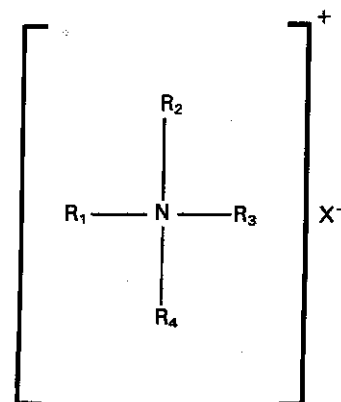
The chemical formula for quaternary ammonium compounds is shown in Figure 41.5.

These cationic surface-active compounds are, as their name implies, derivatives of an ammonium halide in which the hydrogen atoms are substituted by at least one lipophilic group, a long-chain alkyl or aryl-alkyl radical containing C_8 - C_{18} carbon atoms. In marked contrast to phenol and the cresols these compounds are mild in use and active at such high dilutions as to be virtually non-toxic. Their surface-active properties make them powerful cleansing agents, a useful adjunct to their common use as skin antiseptics and preservatives in contact lens cleansing and soaking solutions. They are also safe for formulating into eye drops and injections, and are widely used in gynaecology and general surgery. Active as cations, ambient pH is important, as is interference caused by anions. Thus, alkaline conditions promote activity and it is important that all traces of soap, which is anion active, are removed from the skin prior to treatment with a quaternary ammonium compound. Foreign organic matter and grease also cause inactivation.

One effect of the detergent properties of these compounds is to interfere with cell permeability such that susceptible bacteria - mainly the Gram-positive groups - leak their contents and eventually undergo lysis. Gram-negative bacteria are less susceptible and, to widen the spectrum to include these, mixtures of quaternary ammonium compounds with other antimicrobial agents such as phenoxethanol or chlorhexidine are used.

Biguanides and amidines

Chlorhexidine is a widely used biocide which has activity against Gram-positive and Gram-negative bacteria but has little activity against endospores or viruses (Fig. 41.6). It is widely used in general surgery, both alone and in combination with cetrim-



Cetrimide BP

$R_1R_2R_3-CH_3$

R_4 —mainly $C_{14}H_{29}$

$X-Br$

Benzalkonium Chloride BP

$R_1R_2-CH_3$

$R_3-C_6H_5CH_2$

R_4 —mainly $C_{13}H_{27}$

$X-Cl$

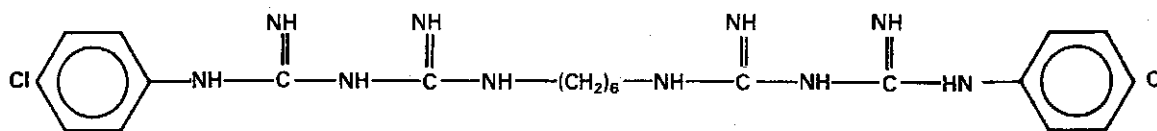
Fig. 41.5 Chemical structure of cetrimide and benzalkonium chloride.

ide, and can also be used as a preservative in eye drops. Polyhexamethylene biguanide (PHMB) is a polymeric biguanide used widely in the food, brewing and dairy industries, and has also found application as a disinfectant in contact lens cleaning solutions. The biguanides act on the cytoplasmic membrane, causing leakage of intracellular constituents.

The aromatic diamidines, propamidines and dibromopropamidines, are non-toxic antiseptics mainly active against Gram-positive bacteria and fungi. However, resistance to these agents can develop quickly during use.

The halogens and their compounds

Chlorine gas is a powerful disinfectant used in the municipal treatment of drinking water and in swimming baths. Solutions of chlorine in water may be made powerful enough for use as general household bleach, and disinfectant and dilute solutions are



Chlorhexidine

Fig. 41.6 Chemical structure of chlorhexidine.

used for domestic hygiene. Unionized hypochlorous acid (HOCl) is an extremely potent and widely used bactericidal agent which acts as a non-selective oxidant, reacting readily with a variety of cellular targets. Well-known pharmaceutical formulations containing chlorine are Eusol (Chlorinated Lime and Boric Acid Solution BPC 1973) and Dakin's Solution (Surgical Chlorinated Soda Solution BPC 1973), both of which are designed to provide slow release of chlorine.

An alternative method of obtaining more prolonged release of chlorine is by the use of organic chlorine compounds such as Chloramine T (sodium *p*-toluene-sulphonchloramide) and Halazone BPC 1973 (*p*-sulphondichloramide benzoic acid), the former used as a skin antiseptic and the latter for treating contaminated drinking water. The high chemical reactivity of chlorine renders it lethal to bacteria, fungi and viruses, and to some extent spores and this activity is optimal at acid pH levels around 5.0.

Iodine, like chlorine a highly reactive element, denatures cell proteins and essential enzymes by its powerful oxidative effects. Traditionally it has been used in alcoholic solutions such as Tincture of Iodine (BP 1973) or complexed with potassium iodide to form an aqueous solution (Lugol's Iodine BP 1973). The staining and irritant properties of iodine have resulted in the development of iodophores, mixtures of iodine with surface-active agents, which hold the iodine in micellar combination from which it is released slowly. Such a preparation is Betadine (polyvinylpyrrolidone-iodine), used as a non-staining, non-irritant antiseptic.

Metals

Many metallic ions are toxic to essential enzyme systems, particularly those utilizing thiol ($-\text{SH}$) groups, but those used medically are restricted to mercury, silver and aluminium. The extreme toxicity of mercury has rendered its use obsolete apart from in organic combination. The organic compounds that still have a limited use in pharmacy are phenylmercuric nitrate (and acetate) as a bactericide in eye drops and injections, and thiomersal (sodium ethylmercurithiosalicylate) as a preservative in biological products and certain eye drops.

Silver, in the form of the nitrate, has been used to treat infections of the eyes, as have silver protein

solutions. Aluminium foil has been used as a wound covering in the treatment of burns and venous ulcers, and has been shown to adsorb micro-organisms and inhibit their growth.

The acridines

This group of compounds interferes specifically with nucleic acid function and has some ideal antiseptic properties, thus aminacrine hydrochloride is non-toxic, non-irritant, non-staining and active against Gram-positive and Gram-negative bacteria even in the presence of serum.

This brief survey has given some indication of the variety of antimicrobial compounds available. Each of these has a defined spectrum of utility and in the correct conditions of use can substantially contribute to the control of microbial proliferation and infection.

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