SURFACTANT SYSTEMS

Their chemistry, pharmacy and biology

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Preface

It is now twelve years since *Solubilization by Surface-Active Agents* appeared. Since the publication of that monograph the subject has expanded rapidly as the unique potential of surfactants has become known to a wider circle of scientists. In a recent review Menger (*Accounts of Chemical Research*, **12** (1979) 111) estimated that since 1970 there have been over 2800 publications on micelles and micellization alone. The topic of catalysis in micellar media was in an early stage of development in 1968 but the growth in this subject has given rise to an excellent textbook by Fendler and Fendler. We have felt for some time that a revision of *Solubilization by Surface-Active Agents* was overdue. The book has been out of print for some time. Owing to pressure of other work, Professor P. H. Elworthy and Dr C. B. Macfarlane were unable to undertake the work of revision but while working together on an undergraduate textbook the present authors decided to set to work, realizing both the impossibility of producing a comprehensive textbook and the need to alter the scope of the book.

Micellar solubilization occurs over a relatively small surfactant concentration range; because of this and because the phenomenon is never observed in isolation, we have extended the text to include surface activity, emulsions and suspensions and, as our emphasis is on formulation of medicinal products, to the difficult topic of the toxicology of surface-active agents. It is clearly not possible to produce a text which reviews all of these areas in great detail; what we have attempted to do is to deal with those aspects of the subject matter which are relevant in the formulation and use of surfactants in pharmacy and in formulation of products for human and animal use. The consequences of the inclusion of surfactants into such formulations is considered in some detail. The field is widened to include discussion of related problems of the use of surfactant formulations in agriculture and horticulture. Since 1968 there has been an increased awareness of the potential and limitations of surfactant systems.

Wherever possible we have attempted to give a greater quantitative emphasis to the treatment of topics than was perhaps evident in the original textbook. The book is, however, aimed at the same audience, final year students of pharmacy especially those specializing in pharmaceutics and pharmaceutical technology, postgraduate students of pharmacy, biochemistry, biology, chemistry, and those working in industrial research and development laboratories exploring the value or problems of surfactant systems. As we are both based in Schools of

Pharmacy our emphasis is on surfactant systems containing biologically active molecules, but the problems experienced in pharmaceutical systems are not unique and we hope that our treatment of the subject matter will be of interest to those working in many other spheres of activity. Biochemists, especially those working on membrane structure and function, have long been aware of the selective solubilizing power of surfactants for membrane components; chemists now know that surfactants can modify chemical reactions; pharmaceutical scientists are aware of the formulation potential of surfactants. Here we try to put these threads together and to discuss the newer developments in surfactant technology which will allow even greater progress in the future.

We are grateful to Professor Elworthy and Dr Macfarlane for allowing us to use portions of the original text, although comparatively little of the original remains, and for their encouragement to pursue the rewriting. We would welcome receiving from workers in the field copies of their published work especially if it is felt that we have neglected an area or misinterpreted their viewpoint.

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Contents

1 *Surface activity*

A surface-active agent is, as the name implies, a compound which will adsorb at an air–water or oil–water interface and at the surface of solids. The structural features of these molecules which are responsible for surface activity are examined in this chapter and some of the factors which influence the extent of adsorption are considered. A study of the adsorption process is of fundamental importance in an understanding of the properties of surface-active compounds since, as we will discuss in later chapters, it is the change in interfacial free energy and surface charge resulting from adsorption which leads to the ability of these compounds to act as emulsifying and suspending agents. A survey of the wide variety of surfactants which are used in pharmaceutical systems is included in the chapter, together with a brief indication of the many and diverse uses of this versatile group of compounds.

1.1 Amphipathic molecules

Surface-active agents are characterized by the possession of both polar and non-polar regions on the same molecule. The polar or hydrophilic region of the molecule may carry a positive or negative charge, giving rise to cationic or anionic surfactants, respectively, or may be composed of a polyoxyethylene chain, as in most of the non-ionic surfactants. The non-polar or hydrophobic portion of the molecule is most commonly a flexible chain hydrocarbon although there is a large number of compounds including many molecules of biological interest, with aromatic hydrophobic groups. The dual nature of a surfactant is typified by sodium dodecyl sulphate (NaDS):

$$\underbrace{CH_3.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2.CH_2}_{\text{hydrophobic}}.\underbrace{SO_4^-Na^+}_{\text{hydrophilic}}.$$

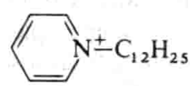
The existence in the same molecule of two moieties, one of which has affinity for solvent and the other of which is antipathetic to it, is termed amphipathy. This dual nature is responsible for the phenomenon of surface activity, and of micellization and solubilization. As a class these substances, which include soaps and detergents, can be called association colloids, a name indicating their

tendency to associate in solution, forming particles of colloidal dimensions. Owing to their tendency to become adsorbed at interfaces, they are often called surface-active agents or colloidal surfactants. Typical examples of the main classes of surfactants are:

(1) *Anionic.* The anion is the surface-active species, e.g.

Potassium laurate	$CH_3(CH_2)_{10}COO^-$	K^+
Sodium dodecyl (lauryl) sulphate	$CH_3(CH_2)_{11}SO_4^-$	Na^+
Hexadecylsulphonic acid	$CH_3(CH_2)_{15}SO_3^-$	H^+
Sodium dioctylsulphosuccinate	$C_8H_{17}OOCCHSO_3^-$ | $C_8H_{17}OOCCH_2$	Na^+

(2) *Cationic.* The cation of the compound is the surface-active species, e.g.

Hexadecyl(cetyl)trimethylammonium bromide	$CH_3(CH_2)_{15}N^+(CH_3)_3$	Br^-
Dodecylpyridinium chloride		Cl^-
Dodecylamine hydrochloride	$CH_3(CH_2)_{11}\overset{+}{N}H_3$	Cl^-

(3) *Ampholytic.* This type can behave as either an anionic, non-ionic, or cationic species, depending on the pH of the solution. The zwitterionic form of *N*-dodecyl-*N*,*N*-dimethyl betaine is:

$$C_{12}H_{25}N^+(CH_3)_2CH_2COO^-$$

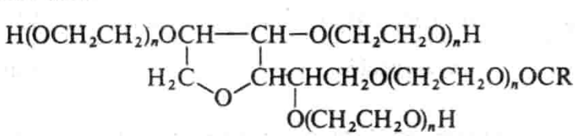
(4) *Non-ionic.* The water-soluble moiety of this type can contain hydroxyl groups or a polyoxyethylene chain, e.g. polyoxyethylene *p-tert*octylphenyl ether:

$$C_8H_{17}C_6H_4O(CH_2CH_2O)_{10}H$$

Polyoxyethylene monohexadecyl ether:

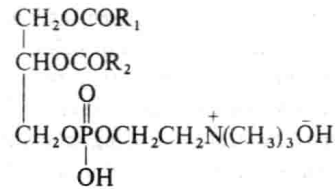
$$CH_3(CH_2)_{15}(OCH_2CH_2)_{21}OH$$

Fatty acid esters of anhydrous sorbitols which have been treated with ethylene oxide are also used:

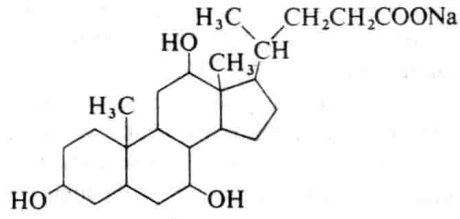


where R is the hydrocarbon part of the fatty acid chain.

(5) *Naturally occurring compounds.* Phosphatides are surface-active agents, e.g. lecithin: dialkylglycerylphosphorylcholine:



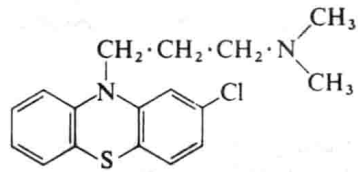
where R_1 and R_2 represent fatty acid residues, generally C_{12}–C_{18}, depending on the source. Lysolecithin, with one fatty acid residue removed, is more water soluble. The lecithins are believed to play some part in the transport of water-insoluble compounds *in vivo*. Cholic acid and desoxycholic acid are the most important of the naturally occurring bile acids, which also behave as association colloids.



Sodium cholate

The micelles formed by these perhydrocyclopentophenanthrene derivatives have an important biological role.

(6) *Drugs.* A large number of drugs are surface active including the phenothiazine derivatives, e.g. chlorpromazine, diphenylmethane derivatives e.g. diphenhydramine, and tricyclic antidepressants e.g. amitriptyline.



Chlorpromazine

The biological and pharmaceutical consequences of the surface activity and association behaviour of drugs is discussed in Chapter 4.

1.1.1 General properties of some surfactants of pharmaceutical interest

(A) ANIONIC SURFACE-ACTIVE AGENTS

(i) Soaps

The most commonly used soaps are the alkali-metal soaps, *R*COOX where X is sodium, potassium or ammonium. The chain length, *R*, of the fatty acid is generally between C_{10} and C_{20}. Lower members of the series possess little surface activity, whilst higher members are not sufficiently soluble in water to be of use.

Soaps are unstable in acid media since the free fatty acid formed under these conditions will tend to be insoluble. Alkali-metal soaps are used in the preparation of oil-in-water emulsions, which are most stable in alkaline solution (above pH 10) and which crack in acid media and in the presence of calcium ions. Water-in-oil emulsions may be prepared using calcium, zinc, magnesium and aluminium salts of the higher fatty acids – the so-called metallic soaps. The combination of amine salts such as triethanolamine, with fatty acids gives the amine soaps. These soaps yield oil-in-water emulsions which are more stable than those prepared with alkali-metal soaps, although they still tend to crack in acid conditions.

(ii) Sulphated fatty alcohols

These are salts (usually sodium) of the sulphuric esters of the higher fatty acids. The most common example is sodium lauryl sulphate B.P. which is a mixture of sodium alkyl sulphates, the chief of which is sodium dodecyl sulphate $C_{12}H_{25}SO_4^-Na^+$. Sodium lauryl sulphate is used pharmaceutically as a pre-operative skin cleanser, having bacteriostatic action against gram-positive bacteria, and also in medicated shampoos. The lower chain length compounds around C_{12} have better wetting properties whilst the higher members, C_{16}–C_{20} have better detergent properties. Triethanolamine and ammonium salts are used in hair shampoos and cosmetics. The sulphated fatty alcohols generally retain their properties over a wide pH range.

(iii) Sulphated polyoxyethylated alcohols

These compounds have the general formula $R(OCH_2CH_2)_xSO_4^-M^+$. The oxyethylene chain length x is usually less than 6. They are similar in properties to the sulphated fatty alcohols but have the advantage of better aqueous solubility, better resistance to electrolytes and water hardness and are generally less irritant to the skin and eyes.

(iv) Sulphated oils

These are prepared by treating fixed oils, for example castor oil, (which contains the triglyceride of the fatty acid 12-hydroxyoleic acid) with sulphuric acid and neutralizing with sodium hydroxide solution. Sulphated castor oil is used pharmaceutically as an emulsifying agent for oil-in-water creams and ointments. It is non-irritant and is used as a cleansing agent when soap is contra-indicated. It is also used in the manufacture of shampoos and deodorant sprays.

(B) CATIONIC SURFACE-ACTIVE AGENTS

The main types of cationic surfactants of pharmaceutical importance have hydrocarbon chains containing between 8 and 18 carbon atoms to which are attached amine, pyridinium or piperidinium groups. There is an important difference between the effect of pH on the properties of the primary, secondary and tertiary amines and on those of the quaternary amines. Whilst the quaternary amines are ionized at all pH values, the other classes of amine are fully charged

only at pH values up to within two pH units of their pK_a which is typically between pH 8 to 10. Since the uncharged forms of the majority of cationic surfactants are insoluble in water, most long chain non-quaternary amines precipitate out of solution at alkaline pH. Piperidinium derivatives may have two pK_a values and hence may exist as a single or doubly charged compound depending on the pH.

Cationic surfactants are important pharmaceutically because of their bactericidal activity against a wide range of gram-positive and some gram-negative organisms. They may be used on the skin especially in the cleansing of wounds. Aqueous solutions are used for cleaning contaminated utensils. Cationic surfactants may be used as emulsifying agents in the formation of oil-in-water creams and lotions into which may be incorporated cationic or non-ionic ingredients. They may also be used as preservatives. Some of the more important cationic surfactants of pharmaceutical importance are:

(i) Cetrimide B.P.

This is a mixture consisting mainly of tetradecyl (approximately 68%), dodecyl (approximately 22%) and hexadecyltrimethylammonium bromides (approximately 7%). Solutions containing 0.1 to 1 per cent of Cetrimide are used for cleansing the skin, wounds and burns, for cleaning contaminated vessels, for storage of sterilized surgical instruments and for cleaning polythene tubing and catheters. Solutions of Cetrimide are also used in shampoos to remove scales in seborrhoea. In the form of Cetrimide emulsifying wax it is used as an emulsifying agent for producing oil-in-water creams.

(ii) Benzalkonium chloride

This is a mixture of alkylbenzyldimethylammonium chlorides of the general formula $[C_6H_5CH_2\overset{+}{N}(CH_3)_2R]Cl^-$ where R represents a mixture of the alkyls from C_8H_{17} to $C_{18}H_{37}$. In dilute solution (1 in 1000 to 1 in 2000) it may be used for the pre-operative disinfection of skin and mucous membranes, for application to burns and wounds and for cleansing polythene and nylon tubing and catheters. Benzalkonium chloride is also used as a preservative for eye-drops of the B.P.C. and U.S.N.F.

(c) NON-IONIC SURFACE-ACTIVE AGENTS

Non-ionic surfactants have the advantage over ionic surfactants in that they are compatible with all other types of surfactant and their properties are generally little affected by pH. However, aqueous solutions of some non-ionic surfactants may become turbid on warming as the cloud point is exceeded.

The amphiphilic nature of non-ionic surfactants may be expressed in terms of the balance between the hydrophobic and hydrophilic portions of the molecule. An empirical scale of HLB (hydrophile–lipophile balance) numbers was devised by Griffin which is useful in the selection of a surfactant mixture for the emulsification of a particular oil (see Chapter 8). Although applied mainly to non-ionic surfactants, the HLB system may also be used for ionic surfactants. For

non-ionic surfactants, HLB values range from 0 to 20 on an arbitrary scale. T lower the HLB number, the more lipophilic is the compound and vice versa. HI values are quoted in Table 1.1 and 1.2 for some commonly used non-ior surfactants.

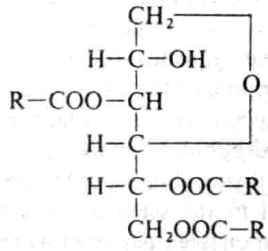
Table 1.1 HLB values of sorbitan esters

Chemical name	Commercial name	HLB
Sorbitan monolaurate	Span 20	8.6
Sorbitan monopalmitate	Span 40	6.7
Sorbitan monostearate	Span 60	4.7
Sorbitan tristearate	Span 65	2.1
Sorbitan mono-oleate	Span 80	4.3
Sorbitan tri-oleate	Span 85	1.8

Table 1.2 HLB values of polysorbates

Chemical name	Commercial name	HLB
Polyoxyethylene (20) sorbitan monolaurate	Polysorbate (Tween) 20	16.7
Polyoxyethylene (20) sorbitan monopalmitate	Polysorbate (Tween) 40	15.6
Polyoxyethylene (20) sorbitan monostearate	Polysorbate (Tween) 60	14.9
Polyoxyethylene (20) sorbitan tristearate	Polysorbate (Tween) 65	10.5
Polyoxyethylene (20) sorbitan mono-oleate	Polysorbate (Tween) 80	15.0
Polyoxyethylene (20) sorbitan tri-oleate	Polysorbate (Tween) 85	11.0

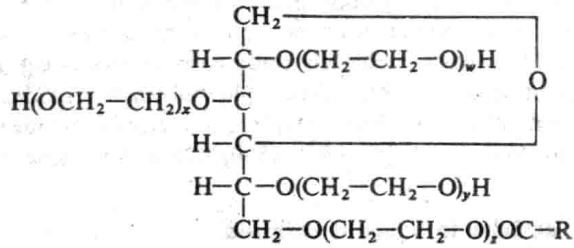
(i) Sorbitan esters



where R is H or an alkyl chain

The commercial products are mixtures of the partial esters of sorbitol and its mono- and di-anhydrides with oleic acid. The formula of a representative component is shown above. They are generally insoluble in water and are used as water-in-oil emulsifiers and as wetting agents. The main sorbitan esters are listed in Table 1.1.

(ii) Polysorbates



where $n = x + w + z + 2$ and R is an alkyl chain

Commercial products are complex mixtures of partial esters of sorbitol and its mono- and di-anhydrides condensed with an approximate number of moles of ethylene oxide. The formula of a representative component is shown above. The polysorbates are miscible with water, as reflected in their higher HLB values (see Table 1.2), and are used as emulsifying agents for oil-in-water emulsions.

(iii) Polyoxyethylated glycol monoethers

We may represent the structure of these compounds by the general formula C_xE_y where x and y denote the alkyl and ethylene oxide chain lengths, respectively, e.g. $C_{16}E_7$ represents heptaoxyethylene glycol monohexadecyl ether.

Cetomacrogol 1000 B.P.C. is a water-soluble compound with an alkyl chain length of 15 or 17 and an oxyethylene chain length of between 20 and 24. It is used in the form of cetomacrogol emulsifying wax in the preparation of oil-in-water emulsions and also as a solubilizing agent for volatile oils.

Other polyoxyethylated glycol monoethers are commercially available as the Brij series (Atlas) which includes polyoxyethylene lauryl ethers (Brij 30, 35) cetyl ethers (Brij 52, 56, 58), stearyl ethers (Brij 72, 76, 78) and oleyl ethers (Brij 92, 96, 98).

(iv) Polyoxyethylated alkyl phenols

Polyoxyethylated nonylphenols are available commercially as the Igepal Co series with a wide range of oxyethylene chain lengths from 1.5 to 100. Detergents with low oxyethylene chain lengths are water-insoluble and are water-in-oil emulsifying agents, longer oxyethylene chain length compounds are water-

soluble and produce oil-in-water emulsions. Polyoxyethylated *t*-octylphenols are available as the Triton-X series which includes X-114 (E_{7-8}); X-100 (E_{9-10}) and X-102 (E_{12-13}).

(v) Poloxamers

These are polyoxyethylene–polyoxypropylene derivatives with the general formula $HO(CH_2.CH_2.O)_a\ (CH_2.CH(CH_3)O)_b\ (CH_2.CH_2.O)_cH$ where $a = c$. The polyoxypropylene hydrophobic groups —$(CH_2CH(CH_3)O)$ and the polyoxyethylene hydrophilic groups of these compounds may be varied over a wide range to give compounds with the required properties. These compounds are commercially available under the trade name *Pluronic*, e.g. *Pluronic* F68: Polyoxypropylene (mol. wt. 1501–1800) + 140 mol ethylene oxide; *Pluronic* L62: polyoxypropylene (mol. wt. 1501–1800) + 15 mol ethylene oxide; and *Pluronic* L64: polyoxypropylene (mol. wt. 1501–1800) + 25 mol ethylene oxide.

1.2 Surface activity in aqueous solution

Two processes have an important influence on the surface activity in aqueous solution. One concerns the effect which a solute has on the structure of water and the other concerns the freedom of motion of the hydrophobic groups.

Many of the current theories of water structure are based on the premise that water is composed of both structured regions, in which the water molecules are hydrogen-bonded together in a tetrahedral arrangement similar to that of ice, and also regions of free, unbound molecules. The continuous reorientation of water molecules resulting in the destruction and reconstruction of ordered regions has led to the apt description of this particular model as the 'flickering cluster' model of water structure [1]. The solution of an amphiphilic molecule in pure water is accompanied by an initial disruption or distortion of the hydrogen bonds as the molecule is accommodated into the highly structured network. In the case of the hydrophobic region of the molecule there is usually no possibility of hydrogen bonding with water molecules to compensate for this bond disruption. Experimental evidence from proton spin relaxation times [2] and elastic neutron scattering suggests that the water molecules in the immediate vicinity of the hydrocarbon chain restructure into an even more ordered arrangement than in pure water. This phenomenon has been termed 'hydrophobic hydration'. The overall effect is of an entropy decrease making the dissolution of hydrocarbon an unfavourable process. The hydrocarbon chain of the amphiphile is brought into solution by virtue of its attachment to a hydrophilic group, either a polar head group as in ionic surfactants, or an oxyethylene chain as in most non-ionic surfactants. Both of these groups are able to form strong hydrogen bonds with the water molecules which more than compensate energetically for the initial disruption process.

The amphiphile in solution may be thought of as being surrounded by a cage of highly structured water. A consequence of this situation is that the internal torsional vibrations of the hydrocarbon chains are restricted in solution as indeed