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Review Article

Solubilized Systems in Pharmacy

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SOLUBILIZED SYSTEMS were originally described by McBain (1) as those in which the solubility of materials otherwise insoluble, or only poorly soluble, in a given media is increased due to the prior presence of particles of colloidal dimensions, termed *micelles*. It is now well established that these micelles arise from the aggregation of molecules containing distinct regions of opposing hydrophilic and lipophilic solvent tendencies. Such molecules have been variously described as surface-active agents, surfactants, or amphiphiles (2). While the term *solubilization* is generally applied to the solution of predominantly lipophilic molecules in aqueous surfactant solutions, it may be equally well applied to the solution of hydrophilic molecules in nonaqueous surfactant solutions which contain reversed micelles (3, 4). Unfortunately, the terms *solubilization* and *solubilized system* have, in recent years, been applied to the solution of materials by mechanisms other than those involving the presence of micelles. Work reviewed elsewhere in this article clearly shows that the biological activity of materials dissolved in aqueous surfactant solutions depends, not on the total concentration, but on the concentration in the aqueous continuous phase, as distinct from that in the micellar *pseudo*phase. The greater the distribution in favor of the micellar pseudophase, the lower the activity. For this reason, if for no other, a distinction should therefore be drawn between an increase in solubility due to the presence of micelles and an increase achieved by other means, such as the addition of large amounts of water-miscible organic solvents. Accordingly, this article will consider only those systems in which increased solubility of the material is due to micellar solubilization. No account will be given of the extensive use of surface-active agents to produce emulsions of pharmaceutical interest, although it should be appreciated that the separated, individual phases of such dispersions are in fact examples of solubilized systems. It is as well to emphasize also, at this point, that micellar solutions are thermodynamically stable systems (5), whereas emulsions are thermodynamically unstable systems. The view that solubilization is a special classification of emulsification is therefore erroneous, and the use of such terms as *microemulsions* when considering solubilization is highly misleading.

For many years (6), surface-active agents have been used as a means of producing aqueous solutions of phenols, and as early as 1928 Hampil (7) observed that certain soaps reduced the antimicrobial activity of phenol. It was only after World War II, however, when nonionic surfactants of low systemic toxicity became commercially available, that surfactants began to be widely used in pharmaceutical practice to prepare solubilized systems, particularly those intended for internal use. Ekwall and Sjöblom (8) in 1949 solubilized such steroid hormones as

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TABLE I.—SOME MATERIALS OF PHARMACEUTICAL IMPORTANCE FORMULATED AS SOLUBILIZED SYSTEMS

Compound	Surface-Active Agent, Type	Ref.
Acetomenaphthone	Nonionic[a]	(9)
21-Acetoxypregnenolone	Nonionic[a]	(10)
Acetylsalicylic acid	Anionic, cationic, nonionic	(11)
Aromatic waters	Nonionics[a,b]	(12, 13)
Benzocaine	Anionic, cationic, nonionic[b]	(14)
Benzoic acid derivatives	Nonionics[b]	(15)
Benzylchlorophenol	Anionic	(16)
Chloramphenicol	Nonionic[a]	(21)
Chloroform	Licorice[a]	(17)
Chlorotrianisene	Nonionic[a]	(9)
Chloroxylenol	Anionic, nonionic[b]	(18, 19)
Choline derivatives	Anionic	(20)
Cortisone acetate	Nonionic[a]	(9)
Cyclocoumarol	Nonionic[a]	(9)
Desoxycorticosterone acetate	Anionics, nonionics[a]	(8–10, 22)
Dicoumarol	Nonionic[a]	(9)
Dienestrol	Nonionic[a]	(9)
Diethylstilbestrol	Nonionic[a]	(9)
Digitoxin	Nonionic[a]	(9)
Essential oils	Nonionics[a]	(23, 24)
Estradiol	Anionic	(8, 22)
Estrone	Anionic, cationic, nonionic[a]	(25)
Ethylbiscoumacetate	Nonionic[a]	(9)
Fluorometholone	Nonionic	(26)
Hexestrol	Nonionic[a]	(9)
Iodine	Nonionics[b]	(27, 28)
Methylprednisolone	Nonionic	(26)
Methyltestosterone	Nonionics[a]	(9, 10)
Phenobarbital	Nonionic[a]	(29)
Progesterone	Anionic, nonionics[a]	(9, 10, 22)
Testosterone	Anionics, nonionic[a]	(8, 10)
Tyrothricin	Nonionic[a]	(9)
Vitamin A (free alcohol and esters)	Nonionics[a,c]	(9, 30, 31)
Vitamin D	Nonionics[a,c]	(9, 31)
Vitamin E (free alcohol and esters)	Nonionics[a,c]	(9, 31)
Vitamin K	Nonionic[a]	(9)

[a] Polyoxyethylene sorbitan fatty acid esters. [b] Polyoxyethylene monoalkyl ethers. [c] Sucrose monoesters.

testosterone, estrone, hexestrol, and desoxycorticosterone by the use of several different surfactants. Since that date, an increasing number of solubilized products have either been proposed or produced, as Table I clearly shows. Surface-active agents have also been used to facilitate the preparation and improve the stability and dilution properties of several galenicals (32–35). Other workers (36, 37) have employed the solubilizing action of nonionic agents to overcome incompatibilities; a nonionic surfactant has also been used to clarify such preparations as syrup of ginger which normally contain a small amount of insoluble matter (13). More recently, the solubilizing properties of licorice toward chloroform and volatile oils have been studied (17). The solubilization of perfume materials has also been investigated (38, 39). The pharmaceutical significance of solubilization in nonpolar solvents has been discussed by Higuchi and Misra (40).

While the great majority of work concerned with investigating the factors that influence solubilization has been undertaken on nonpharmaceutical systems, the results obtained are wholly applicable to pharmacy. Although these studies have been comprehensively summarized (2, 4, 6, 41–43), a brief account is included here for the sake of completeness.

The existence of micelles was first deduced by conductivity and osmotic studies (44, 45), the concentration at which this aggregation occurred (the critical micelle concentration or CMC) being readily determined by a number of physicochemical techniques (4, 46). Since the solubilization of materials is dependent on the presence of micelles, those factors which influence the CMC are of obvious importance. Various workers have studied the effect of surfactant chain length on the CMC in binary surfactant–water systems; with most ionic surfactants, an increase of two carbon atoms in the alkyl chain leads to a fourfold decrease in the CMC (47, 48). Nonionic (49, 50) and ampholytic (51, 52) surface-active agents of corresponding alkyl chain length show lower CMC's. While hydrocarbons have only a small effect on the CMC (53–55), the addition of polar organic molecules produces ternary systems in which the CMC is frequently different from that in the original binary system. In the num-

erous systems that have been studied (55–58), the CMC generally decreases as a function of the polar additive concentration, although water-miscible polar molecules exert the opposite effect (59, 60). The addition of electrolytes also reduces the CMC (2, 4).

A clear distinction must be made between the CMC in binary surfactant–water systems and that in ternary surfactant–water–additive systems, even though in certain cases the difference between the two values will be insignificant. Failure to use the correct value when interpreting solubilization data shows a lack of appreciation for the mechanics of solubilization and the properties of amphiphilic molecules.

Although there is general agreement that micelles exist in surfactant solutions, there is still some measure of disagreement concerning the shape and size of these aggregates (2, 4, 42). However, because of the formation of conjugate liquid crystalline phases upon saturation of the isotropic liquid phase in a large number of binary (61–63) and ternary (62–65) systems, the views expressed by Winsor (2) seem most logical. Winsor believes that increasing the surface-active agent concentration leads, at the CMC, to the formation of spherical micelles of the Hartley type (66). At higher concentrations there is a progressive change to a planar form, comparable to the McBain lamellar micelle (67) which, when it has achieved a certain extension and stability, appears as a separate liquid crystalline phase. This latter is an anisotropic phase, intermediate in structure between the liquid and crystalline states; the molecules possess an ordered laminar arrangement. Lawrence[1] (68), in 1937, was the first to distinguish between the different sites that various solubilized molecules would occupy on or within the micelle depending on their relative hydrophilic and lipophilic tendencies. X-ray studies (69–74) support Lawrence's contention that nonpolar organic materials are solubilized in the hydrocarbon interior of the micelle and that polar molecules penetrate into the micellar palisade layer. Conductivity (75), spectrophotometric (76), and more recently, nuclear magnetic resonance studies (77, 78) also provide evidence that solubilization occurs at different sites in or on the micelle.

The production of a liquid crystalline phase by the use of organic liquids, termed *lyotropic mesomorphism* (80), may be thought of as a special example of solubilization. The pharmaceutical applications of this phase have not yet been exploited, even though its properties (81, 82) would appear to offer certain advantages over the conventional solubilized liquid-type systems—for example, reduced rates of autoxidation of susceptible materials (83, 84).

[1] It is regrettable that the priority for establishing this concept is frequently given in the literature to other workers (41, 79). This is incorrect, since Lawrence's paper predates these by at least a decade.

FORMULATION OF SOLUBILIZED SYSTEMS

The solubilized systems used in pharmacy today can be broadly divided into those intended for internal use and those designed for external applications. While surfactants have been used to achieve solubilization in a large number of systems, the two groups of drugs most frequently formulated in this way are the oil-soluble vitamins and steroids and the antimicrobial preparations containing materials of limited aqueous solubility. In the former case, this has been done primarily because of the increased biological activity resulting from enhanced absorption. The improved appearance and the masking of oily tastes constitute important aesthetic considerations. Solubilization is a useful approach when it is desired to administer oil-soluble and water-soluble materials simultaneously, as in the case of multivitamin preparations (85, 86).

Surface-active agents have a twofold effect when used in the preparation of antimicrobial products. Thus, they raise the concentration of the active material in solution, *i.e.*, increase the *capacity* (27) of the system and also influence the biological activity of the compound. Frequently, there are other advantages; thus, solubilized iodine preparations are more stable, relatively nonstaining on fabrics and tissues, nontoxic, nonodorous, and readily miscible with water. At the same time they retain the desired antimicrobial activity attributed to iodine (87).

Surface-Active Agents.—At the concentrations employed in aqueous products designed for internal administration, these agents must be nontoxic, good solvents for lipid-soluble materials, miscible with water, stable and compatible with substances to be dissolved, free from disagreeable odor or taste, and not readily volatile (88). As will be seen later, one of the most important considerations is the toxicity of the surfactant. Therefore, of the anionic, cationic, nonionic, and ampholytic types available, only the nonionics are extensively used.

Although a wide range of nonionic surfactants are available, Table I shows that those most frequently employed are the polyoxyethylene sorbitan fatty acid esters and the polyoxyethylene monoalkyl ethers.

Most of the phenolic antimicrobial prepara-

tions are formulated with anionic surfactants, generally the alkali salt of a straight-chain fatty acid that may be prepared *in situ*. In the case of iodophors, the iodine is solubilized usually in aqueous solutions of nonionic agents which, as a general class, are less toxic than the ionic surfactants as well as being more stable carriers of the iodine (89). A satisfactory product has, however, been formulated using a cationic surfactant (90). Cationic surface-active agents are themselves powerful germicides and are frequently used as such (91). There is some evidence to indicate that a chemical reaction can take place along with the solubilization process in iodophors. Thus, Hugo and Newton (28) have observed that raising and then lowering the temperature during manufacture irreversibly increased the amount of iodine taken into solution. Since solubilized systems are thermodynamically stable systems, any temperature-induced change in solubility should be reversible.

Mulley (92) has recently prepared a list of surfactants that have been used pharmaceutically to prepare systems intended for both internal and external use. A comprehensive list of drugs that have been formulated as solubilized systems is also given.

Quantity of Surface-Active Agent.—Since surfactants are frequently expensive and have an undesirable taste, they should be used in the minimum concentration necessary to achieve solution, quite apart from questions of toxicity. Quite often it is found that, over a certain concentration range, the amount of drug or antimicrobial agent that is solubilized increases directly with surfactant concentration once the CMC has been exceeded (15, 25, 26, 63). Phase equilibrium diagrams clearly indicate, however, that in all instances the line representing the solubility limit will eventually depart from linearity (62, 64, 65). Mulley (92) has attempted to relate the solubilizing power of straight-chain alkyl surfactants to the weight or volume of the hydrocarbon interior of the micelle. From the results cited, it would appear that the correlation is only fair, indicating that this is an oversimplified view of micellar solubilization. It also ignores the previously cited evidence for the existence of different sites of solubilization within the micelle. Such an approach has a certain limited value in the preliminary formulation of solubilized systems.

A better approach to finding the required amount of surfactant is to obtain and identify the relevant portions of the ternary phase diagram by carrying out phase equilibria studies. In this way Boon *et al.* (30) working with the system vitamin A–polyoxyethylene sorbitan monooleate–glycerin–water, were able to formulate clear single-phase liquids containing the minimum quantity of surfactant. Glycerin was used in the mixture because earlier work (93) had demonstrated that the nonionic concentration could be halved by its inclusion to the extent of 30% of the final volume. Variations in the extent of the single-phase region were apparent when different batches of the commercial surfactant were employed. This was attributed to the presence of polyoxyethylene chains of varying length, a factor worthy of constant consideration when employing commercial surface-active agents in formulation work. Other workers have determined ternary phase diagrams in studies on pharmaceutical systems formulated with surface-active agents (24, 94), and the method has much to commend it as an aid to overcoming problems associated with formulation. For example, the formulator is able to predict with confidence the effect on the phase equilibria of dilution with one or all of the components in any desired combination or concentration. This information is of obvious importance in the preparation of a concentrated solution that is to be diluted with water, prior to use, to form a second clear liquid.

Hydrophile-Lipophile Balance (HLB).—The effect of HLB (95) has been investigated by Watanabe *et al.* (96), who established the existence of a regular and definite relationship between the HLB value and the solubilizing efficiency. Goodhart and Martin (15) have similarly found that the solubilities of benzoic acid derivatives were greatly increased as the surfactants used became less hydrophilic. Mima (97) showed that when a mixture of two surface-active agents with widely differing HLB values were used, the range of vitamin A and vitamin D solubilized was smaller than when surfactants having small HLB differences were used. Variations in the amount taken into solution were noted between natural and synthetic vitamins. The HLB system has also been employed in studies concerned with the solubilization of essential oils (98).

STABILITY IN SURFACE-ACTIVE AGENT SOLUTIONS

The stability of solubilized products against degradative processes such as autoxidation and hydrolysis is an important aspect that has been treated in a rational manner only recently.

In 1950, Kern and Antoshkiw (99) investigated the autoxidation of vitamin A formulated both

as an oily solution in cottonseed oil and solubilized in an aqueous nonionic surfactant solution. These workers found that the vitamin in the solubilized state was most resistant to oxidation. Similar findings were reported by Coles and Thomas (93), who suggested that this was due to the vitamin being orientated in such a way within the micelle, considered impervious to oxygen, that the hydrophilic portion faced the aqueous phase. In this manner the unsaturated sites on the vitamin molecule would be protected from attack. Patel *et al.* (100) have, on the other hand, reported that the solubilized vitamin A systems they studied decomposed at a faster rate than emulsified systems. These findings have not been confirmed by other workers, suggesting the presence of a specific reaction or contaminant in the systems used. There have been reports that nonionic surfactants (101) and polyethylene glycols (102) contain peroxides which act as catalysts in autoxidative processes. It is possible that the surfactant samples used by Patel actually increased the rate due to the prior presence of peroxides which were solubilized along with the vitamin in the micelles.

The stability of solubilized vitamin A systems following sterilization has been studied (88); there was no appreciable potency loss after 5 months at 25°.

Carless and co-workers (83, 84, 103–105) have conducted a series of basic studies on the autoxidation of model systems using a manometric technique to obtain the oxygen uptake directly. The early studies (103, 104) revealed that solubilized systems oxidized at a much lower rate than emulsified systems; solubilized systems were also less susceptible to the catalytic action of metallic ions. Later work (105) showed that the site of oxidation was the micellar pseudophase. This was confirmed by Swarbrick and Carless (83), who further showed that the rate was dependent on the micellar concentration of material, considered in relation to the micellar surfactant concentration. Lofgren *et al.* (85, 86) have investigated the effect of various parameters upon the relative stability of oral multivitamin preparations containing nonionic surfactants. It was concluded that the concentration of water present, the type of vehicle, and the pH were important factors. No attempt was made to study the effect of surfactant concentration.

The degradation of vitamin A in an oil solution under an inert atmosphere follows first-order kinetics and obeys the Arrhenius equation. Recently, in stability studies on solubilized vitamin A systems, Carstensen (106) found the logarithm of the rate constant to be linear with respect to the water vapor pressure rather than the reciprocal of the absolute temperature, as demanded by the Arrhenius equation.

As long ago as 1918, McBain and Bolam (107) observed that soap solutions protected materials against hydrolysis. However, it was not until 1960, when Riegelman (14) studied the rate of hydrolysis of benzocaine solubilized in a range of surfactants, that quantitative investigations were undertaken. Riegelman found with the nonionic surfactants that the hydroxyl ions apparently penetrate the polyoxyethylene palisade layer of the micelle since hydrolysis took place in this environment as well as in the aqueous phase. With ionic surfactants the low rates suggested that the polar heads of the surfactant molecules shielded the ester from catalysis. At low concentrations of the cationic surface-active agent, the rate of hydrolysis was increased, presumably due to attraction of the hydroxyl ions into the environment containing the ester. In another series of experiments, Nogami and coworkers investigated the effect of surfactants on the hydrolysis of several other materials of pharmaceutical importance. It was found that the hydrolysis of methantheline bromide (108, 109), in the presence of sodium lauryl sulfate, was markedly dependent on pH, the base catalysis being suppressed by the surfactant, whereas the acid catalysis was promoted. This effect was probably due to the attraction and repulsion between the electrical charge on the micelle and the H^+ and OH^- ions, respectively. An increase in either the alkyl chain length or the concentration of the anionic surfactant led to an increase in the stability of the methantheline molecule (20). The stability of a series of choline derivatives was also improved in the presence of sodium lauryl sulfate. The hydrolysis of undissociated aspirin was suppressed in aqueous solutions of anionic, cationic, and nonionic surface-active agents (11). With the drug in the anionic form, only the nonionic surfactant was efficient in reducing the rate of hydrolysis. Nonionic agents have also been shown to be efficient in inhibiting the alkaline hydrolysis of ethyl *p*-hydroxybenzoate. The addition of sodium lauryl sulfate accelerated breakdown (110). In studies concerned with the hydrolysis of anionic surfactants themselves, Nogami *et al.* (111, 112) found the rate to be dependent on pH, surfactant concentration, and alkyl chain length. The effect of concentration has also been studied by Motsavage and Kostenbauder (113), who found

the hydrolysis rate of sodium lauryl sulfate above the CMC to be more than 30 times that below the CMC.

Mitchell (114–116) has also investigated the hydrolysis of esters in the presence of surface-active agents. He found that the degradative rate decreased as the surfactant concentration was increased, even though the ester concentration remained constant. This behavior was attributed to changes in the distribution of the esters in favor of the micellar pseudophase, where the molecules are less accessible to attack by hydrolysis, in agreement with the proposals originally put forward by Allawala and Riegelman (27).

In hydrolysis studies in solubilized systems, it is therefore the concentration of material in the aqueous or nonmicellar phase which influences the rate; in oxidation, it is the concentration of material in the micellar pseudophase that must be taken into account when undertaking rate studies.

ABSORPTION AND BIOLOGICAL ACTIVITY OF SOLUBILIZED MATERIALS

It is frequently found that the use of surface-active agents to prepare micellar solutions of pharmaceutical materials results in an increased absorption and biological activity. Levy (117) has discussed the various mechanisms by which surfactants may modify drug absorption; such factors as the possible effects on the absorbing membrane, interaction with the drug, and modification of the physical properties of the dosage form should all be considered as exerting a possible influence. The factors involved in the activity of antimicrobial agents in solutions of surface-active agents have been dealt with in an excellent article by Allawala and Riegelman (27).

Several studies have been concerned with the intestinal absorption of solubilized vitamin A preparations (118–121). In all cases an increased absorption of the vitamin was observed. Lewis and his group (121) compared the absorption of solubilized and emulsified preparations with that of an oily solution and found the absorption rose as the degree of dispersion of the vitamin was increased. Thus, the solubilized preparation gave the highest blood level, followed by the emulsion and oily solution in that order. Solubilization does not always result in an increased absorption. For example, the solubilization of salicylic acid (122), normally a well-absorbed drug, led to a decrease in activity resulting from a lower level of absorption. The effect of surfactants would seem therefore to be related to the aqueous solubility of the drug and, as a consequence, its distribution between the aqueous and micellar phases. The presence of micellar material is thought to be a factor in the intestinal absorption of lipids (123).

The percutaneous absorption of estrone is enhanced when the steroid is solubilized. Using the potency of an oily solution injected subcutaneously as having an activity equal to 1.0, Sjöblom (25) found the percutaneous activity of solubilized preparations containing moderate concentrations of surfactants to be 0.36 ± 0.02, compared to a value of 0.13 ± 0.02 when solutions of estrone in oils were used. The activity rose to 0.84 ± 0.15 when volatile organic solvents were used to bring the hormone into solution. Since only small differences were obtained when anionic, cationic, and nonionic surfactants were employed, it was concluded that the charge on the micelle had little effect on penetration into the skin. Sjöblom (124) has conducted studies on estradiol-17 and found similar results.

The antimicrobial activity of solubilized products depends on several factors (27), not the least of which is the concentration of surfactant. Bean and Berry (16) reviewed the early work concerned with this subject and studied the antimicrobial activity of benzylchlorophenol and chloroxylenol in aqueous potassium laurate solutions maintained at a constant surfactant/phenol ratio (19, 125). Below the CMC, the activity increased due to an increase in the phenol concentration and a reduction in surface tension which would facilitate adsorption of the phenol onto the bacterial surface. Above the CMC, the activity decreases because the phenol is now distributed between the micellar pseudophase and the aqueous phase. Brudney (126) has suggested that this sequence of events might be explained on the basis of possible changes in solution structure. Further work by Berry *et al.* (127, 128) showed that the antimicrobial activity depended on the degree of saturation of the aqueous phase rather than the concentration in the micellar pseudophase. Similar findings have been reported by other workers using different systems (27, 129–132). Other support for this view comes from the work of Bean *et al.* (133, 134), who have shown that the antimicrobial activities of such compounds in oil–water systems are dependent on their concentration in the aqueous phase.

Allawala and Riegelman (130) found the activity of solubilized iodine preparations also to be controlled by the concentration in the aqueous phase which, in turn, depends on the

relative concentrations of iodine and surfactant and the distribution of iodine between the micellar and aqueous phases. Other workers (132) have shown that, regardless of whether the iodine is present in a surfactant solution or in an ethanol–potassium iodide solution, there is no significant difference in antimicrobial activity when the systems are compared at the same *available* iodine concentration.

The activity of solubilized phenolic antimicrobial preparations vary, upon dilution, both with the type of surfactant used and its original concentration (135). Mulley (92) has advanced an explanation for this effect based on the possible phase equilibria existing in the systems following dilution. This is an excellent example of the advantages inherent in the use of a triangular diagram approach to the wide variety of problems associated with the successful formulation of solubilized products.

Of related interest is the influence of surface-active agents on the activity of phenolic materials employed to preserve emulsions against microbial attack. Wedderburn (136) has summarized the evidence relevant to establishing the mechanism or mechanisms whereby these preservatives are inactivated, especially in relation to their interaction with nonionic surfactants. Micellar solubilization and the formation of molecular complexes of the type described by Higuchi *et al.* (137, 138) have both been proposed as being responsible for inactivation. While complex formation is thought to be important in some systems (18, 139), Evans (140) has suggested recently that the most important factor is micellar solubilization when the nonionic surfactant concentration exceeds the CMC. Certainly the micelles of nonionic agents appear to offer maximum opportunities for the inactivation of preservatives since they afford the possibility for both hydrogen bonding and solubilization. However, in view of the findings discussed earlier with regard to the antimicrobial activity of phenols and iodine and the hydrolysis of esters in aqueous solutions of surface-active agents, solubilization would seem to be the prime factor involved.

TOXICITY OF SOLUBILIZED SYSTEMS

Toxic effects, arising from the use of solubilized systems, may be due to the surface-active agent itself or to an enhanced toxicity of the additive when in the solubilized state. Schwartz *et al.* (43) note that the oral toxicities of surfactants, as judged by their LD_{50}'s, decrease in the order cationic (50 to 500 mg./Kg.), anionic (2 to 8 Gm./Kg.), and nonionic (5 to 50 Gm./Kg.). Certain ampholytic betaines, of the type synthesized by Beckett and Woodward (52), have been found to possess LD_{50} values ranging from 1.33 to 2.50 Gm./Kg., with no trend apparent as the homologous series was ascended (141). Barail (142) and Fitzhugh and Nelson (143) have also studied the chronic oral toxicities of surfactants. The cationic agent, alkyl dimethyl ammonium chloride, was shown to be toxic to rats at a concentration of 0.063%, whereas dioctyl sodium sulfosuccinate was only slightly toxic at a concentration of 1%. At this concentration, sodium lauryl sulfate showed no toxic effects orally. Several workers have conducted studies on the oral ingestion of nonionic surfactants and found them to be relatively inert (144–146). Up to 6 Gm. of some polyoxyethylene sorbitan fatty acid esters have been taken daily for 28 days by humans without any apparent ill effect (147). The toxicity of dioctyl sulfosuccinate, sorbitan monostearate, polyoxyethylene sorbitan fatty acid esters, and polyoxyethylene stearates have been discussed (148). It was concluded that the toxicity of these surfactants would not hinder their use in orally administered preparations.

Surface-active agents are more toxic when administered intravenously, although there is no correlation between oral and intravenous toxicity (149). Anionic and cationic agents are strongly hemolytic (150), which precludes their use in solubilized preparations administered by this route. Intravenous therapy using polyoxyethylene sorbitan monolaurate has however been considered possible (151), and there are several reports in the patent literature (88, 152, 153) referring to the use of nonionics to prepare such solubilized products. The fatty acid sucrose ester, sucrose monomyristate, exhibits toxic effects when administered parenterally (154).

In products designed for external application, the restriction on the choice of surface-active agent due to toxicity considerations is somewhat less severe. Thus, all three major groups have been used, although again the nonionics appear to be preferred because they are less irritant to the skin (155, 156). Again, the quaternary ammonium compounds are foremost in this damaging action at concentrations higher than 1%. Of the anionic surfactants, the alkyl lauryl sulfonates are irritant above 5% and sodium lauryl sulfate above 20%. The nonionic ethers can be damaging above 5%, although certain of the polyoxyethylene sorbitan fatty acid esters are nonirritant when applied to the eye mucosa in 100% concentrations (156). Non-

ionic surface-active agents have been employed successfully to prepare chemically and physically stable aqueous solutions of anti-inflammatory hormones suitable for topical application to the eye, ear, nose, and throat (157, 158). Other surfactants, however—notably the alkyl polyoxyethylene condensates and some fatty acid amine condensates—exert an undesirable anesthetic action on the eye mucosa (159).

It would seem that a certain degree of caution may be necessary in the prolonged use of solubilized products. Ekwall (160) has observed an increase in subcutaneous adipose tissue following the continued application of a polyoxyethylene sorbitan fatty acid ester to the skin which became concentrated in the fat cells. Perhaps more serious are the observations that the solubilization of hydrocarbons apparently potentiates their carcinogenic activity, often to such an extent that this may be used as a method to encourage tumor production in experimental animals (160–162). Such findings have led certain workers (160, 163) to question the prolonged use of preparations containing surfactants, especially where the additive, *e.g.*, coal tar, is thought to be carcinogenic. A more optimistic evaluation of the polyoxyethylene sorbitan fatty acid esters and their derivatives has been given (164).

SUMMARY

The physicochemical properties of surface-active agents in solution have been discussed, with particular reference to the solubilization of materials of pharmaceutical interest. The use of surfactants in the formulation of solubilized systems relevant to pharmacy has been reviewed, and their effect upon the stability, absorption, and biological activity of drugs and pharmaceuticals discussed. Consideration has also been given to the toxicity of surfactants and of the solubilized products prepared therefrom.

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