Surfactant Systems: Their Use in Drug Delivery

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1 Introduction

Molecules or ions which are amphiphilic, that is, contain both a hydrophobic and hydrophilic part, in aqueous solution frequently assemble at interfaces and self-associate in an attempt to sequester their apolar regions from contact with the aqueous phase. This self-association gives rise to a rich variety of phase structures (Figure 1). Aggregation is not, however, just limited to aqueous solution; it is sometimes observed in non-aqueous polar solvents such as ethylene glycol and non-polar solvents such as hexane (in the latter case giving rise to inverse structures).

Over the years several of the phase structures produced by surfactants have been of interest to the pharmaceutical scientist, either as drug vehicles/carriers or more recently as targetting systems. In the former application the surfactant system takes no part in the biodistribution of the drug it carries, acting purely as the vehicle. In the second case the surfactant system in some way 'conveys' the drug to the desired (or target) site in the body and deposits it. Targetting can take one of two forms; namely 'passive' targetting which relies on the natural biodistribution of the carrier, or 'active' targetting in which the carrier is in some way directed to the desired site, frequently by the use of targetting ligands expressed on the surface of the carrier. Both types of targetting have the advantage of protecting the body from any unwanted side-effects of the drug, while at the same time achieving the desired concentration of drug at the target site.

By far the majority of work examining the potential of surfactant systems in drug delivery has explored their use as drug carriers; for example non-ionic micelles have been widely investigated as a means of producing a clear stable solution of a poorly water-soluble drug suitable for intravenous or oral administration.[1,2] However, during the past twenty years or so, as the importance of drug targetting has been realized, a number of surfactant systems, such as phospholipid or non-ionic surfactant vesicles, have been extensively investigated as targetting systems.[3]

Despite all the research into the potential use of surfactant phase structures for drug delivery, such phase structures have not made much of an impact on the formulation scene; there are only a few marketed preparations that could be considered to be drug-containing surfactant systems in either the United Kingdom or the United States. Consequently, the true potential of surfactant formulations, particularly of non-ionic surfactants, has perhaps not been fully realized. In order to appreciate the potential and also the limitations of such systems an understanding of the phase behaviour of surfactants is essential. The following account therefore describes the phase behaviour of surfactants with reference to their physico-chemical properties relevant to their use as drug delivery systems. It also details some of the work performed to date investigating the use of surfactant systems – in particular, those produced from the less toxic non-ionic surfactants – for drug delivery.[1]

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2 Phase Behaviour of Surfactants

2.1 Equilibrium Phase Structures

Although surfactants self-associate in a wide variety of solvents, their state of aggregation varies considerably between solvents (Table 1). As water or a buffered aqueous solution is the usual continuum for most drug delivery systems, it is important to understand (and predict) the range of equilibrium phase structures commonly encountered in such solutions. Mention will be made of the phase structures encountered in other solvents where appropriate.

When a surfactant is dispersed in water just above the limit of its aqueous solubility (*i.e.* above its critical micelle concentration, cmc) it generally aggregates, depending upon its molecular geometry,[5] into one of four types of structure, namely the isotropic micellar phase and the liquid crystalline hexagonal, lamellar, and cubic phases. The aforementioned phases, with the exception of the lamellar phase, can either be in a normal or reverse orientation. Recently, in addition to these commonly encountered phase structures, there has been an increasing number of more unusual aggregates, such as helical bilayers[6] and fibre gels[7] reported.

Upon increasing the surfactant concentration well above the cmc there are generally changes in aggregate or phase structure. The order of phase structures formed upon increasing surfactant concentration generally follows a well-defined sequence (Figure 2) with a 'mirror plane' through the lamellar phase, such that normal phase structures can be considered to be 'oil-in-water', while reverse structures can be thought of as 'water-in-oil'.[8] Most surfactants, however, exhibit only a portion of this sequence, depending upon the aggregate type initially formed at the cmc and the resulting interaggregate forces experienced.[9] Although the same phase structures are observed in other non-aqueous polar solvents, the sequence of phases is sometimes very different and appears to depend both upon the molecular geometry and the nature of the polar head–solvent interactions.

2.1.1 Implications for Drug Delivery

An understanding of the phase behaviour of surfactants is essential for the efficient use of surface active systems in drug delivery. For example, after introduction into the body the surfactant system may, depending upon its route of administration, undergo a large dilution. If the surfactant is diluted below its cmc, precipitation of transported drug may occur. This precipitation may have very serious consequences, especially if

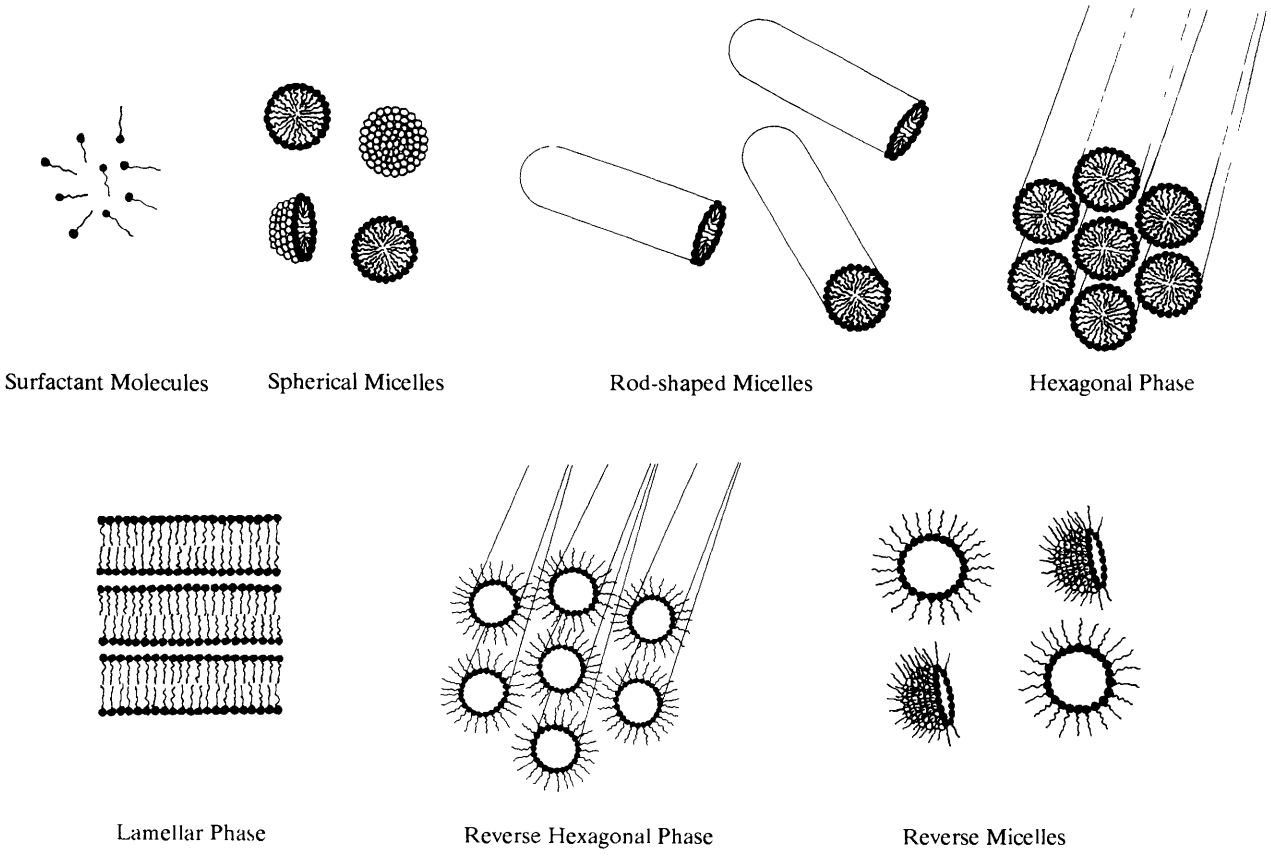

Figure 1

Table 1 Self-association in solvents

Class of solvents	Example of class	Type of Aggregate
Class A	Water, glycerol, ethylene glycol	Normal
Class B	Hexane, benzene, cyclohexane	Reverse
Class C	Methanol, ethanol	No aggregate formation

the drug is being administered intravenously. Ideally therefore the cmc should be a low as possible in order to avoid such problems. Surfactants that form lamellar phases at their cmc generally do so at much lower concentrations than those surfactants which initially form micelles. Since non-ionic surfactants generally exhibit lower cmc's than ionic surfactants they are preferred for the purposes of drug delivery, especially when a micellar solution is being investigated as the drug delivery vehicle. In a similar vein, if a concentrated surfactant solution is administered it may experience a sufficient dilution to induce a phase change, say for example from an hexagonal to a micellar phase. As the drug-carrying capacity of each aggregate type may differ, such a phase change could have very serious implications such as dose dumping within the body. When considering using a surfactant system as a drug delivery vehicle it should also be borne in mind that phase transitions can also be induced by a change in temperature and that normal human body temperature is typically 12 degrees above ambient. Other problems to be aware of are hysteresis effects. These are particularly common in cubic phases and may have important consequences for drug delivery. For example, certain cubic phases have been shown to be pseudo-stable for very long periods at temperatures at which some other form of aggregate would normally be formed.[6]

A knowledge of the various biological surface-active agents which the surfactant aggregate may encounter *in vivo* is also essential as these may alter or even destroy the aggregate. For example the endogenous micelle-forming bile salts encountered in the small intestine have been shown to solubilize orally administered liposomes, thereby releasing any water-soluble solute trapped inside the carrier.

2.3 Modified Phase Structures

In addition to the equilibrium phase structures mentioned above, there are a few non-equilibrium and modified surfactant phase structures that are currently finding application in drug delivery.

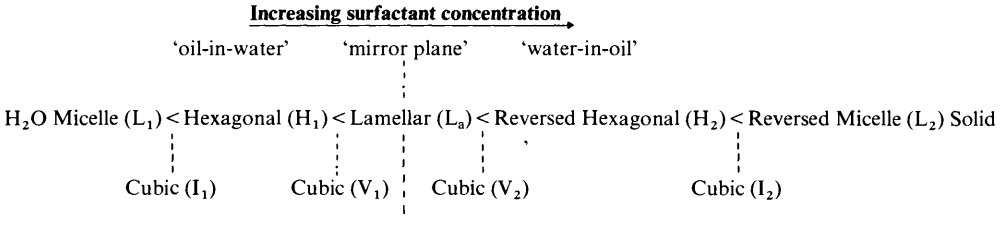

Figure 2 Idealized phase sequence in surfactant–water systems. (Modified from reference 6; terminology as in reference 7.)

2 3 1 Vesicles

Vesicles are generally formed by dispersing lamellar phases in an excess of water[11] (or non-aqueous polar solvents such as ethylene glycol, dimethylformamide), or in the case of reversed vesicles in an excess of oil [12] The resulting vesicles are approximately spherical structures dispersed in a water or an oil continuum Vesicles produced from phospholipids have been widely investigated as drug delivery vehicles Unlike the phase structures mentioned earlier, however, these non-equilibrium structures are prepared using methods such as sonication and will eventually re-equilibrate back into the lamellar phases from which they originate [11] This inherent instability has caused considerable problems with the wide-spread commercial exploitation of vesicular delivery systems For a few surfactants, however, the vesicular phase is an equilibrium structure, for example, the ionic ganglioside GM3, a glucosidic amphiphile of biological origin, forms vesicles spontaneously in water,[13] while some combinations of non-ionic surfactants have been shown to form reversed vesicles spontaneously [14]

2 3 2 Polymerized Aggregates

Attempts have been made to use polymerization to stabilize various nascent phase structures, for example micelles,[15] cubic phases,[16] and vesicles [17] With the exception of micelles (which as yet it has not proven possible to polymerize) polymerization of these structures gives aggregates exhibiting the significant advantage that they do not suffer break down upon dilution *in vivo* However, because of their size (ranging from tens to hundreds of nm) these aggregates can cause problems as they are not readily excreted from the body, hence such systems will probably have limited clinical use, although they may have a use in oral administration In an attempt to overcome the problem, biodegradable polymerized aggregates are presently being investigated [18] When preparing drug-containing polymerized aggregates it is important to choose the appropriate stage for drug addition, adding the drug before polymerization may cause the drug to be irreversibly bound in the aggregate, while addition of the drug after polymerization may lead to low levels of entrapment

2.4 Drug Aggregates

A number of drugs are themselves amphiphilic and may aggregate into various structures, most frequently small micellar type structures [1] In these cases the drug aggregate could act as its own vehicle, if the drug loading were not too high It has been postulated that the formation of vesicles consisting of pure drug (pharmacosomes) should also be feasible [19] Unfortunately most drugs are not lipophilic enough to form vesicles easily without derivatization with materials like fatty acids [19] However with certain drugs it may be possible to produce vesicles over a narrow pH range using the appropriate ratio of amphiphilic salt to free drug The tight control over pH that would be necessary, however, means that such vesicles are unlikely to provide useful drug delivery systems An alternative approach to producing pharmacosomes has recently been reported in which a biodegradable micelle-forming drug conjunct has been synthesized from the hydrophobic drug adriamycin and a polymer composed of polyoxyethylene glycol and polyaspartic acid [20] This approach has the benefit that while it may be possible to dilute out the micelle, the drug will probably not precipitate because of the water solubility of the monomeric drug conjunct Since neither of these types of derivatized drug structures consist of drug alone, they can therefore not be considered to be true drug aggregates

2.5 Influence of Oil

When oil is added to a binary mixture of surfactant and water a whole variety of phase structures may be formed Several of these structures currently have a use in drug delivery, for example microemulsions, macroemulsions, and multiple emulsions [1] Others such as self-emulsifying systems[21] and vesicles encapsulated in water-in-oil emulsions are at present under investigation [22]

3 Choice of Phase Structure for Drug Delivery

When choosing a phase structure for drug delivery a number of factors need to be considered, in particular, how the physicochemical properties of the phase structure relate to the intended application If, for example, a surfactant system is required for topical use the phase structure chosen should be of sufficiently high viscosity to enable the preparation to be retained on the skin surface, while at the same time allowing it to be spread readily over the surface of the skin In contrast, if a system is intended for administration intravenously it should be of sufficiently low viscosity not to cause pain upon injection Another important factor to be considered is the capacity of the aggregate for the drug to be incorporated Micellar solutions, by virtue of low surfactant concentrations, generally exhibit the lowest capacity for drug, while in contrast cubic and other liquid crystalline phases can frequently tolerate very high drug loadings [23 24] Recently it has been realized that the toxicity of a particular surfactant may depend upon the nature of its aggregate For example, the same surfactant has been shown to exhibit a significantly reduced toxicity when present in a vesicular as opposed to a micellar solution

Table 2 gives some of the physico-chemical characteristics important for formulation purposes together with the possible pharmaceutical applications of each phase structure It should be noted that while Table 2 gives the average properties of each phase, the variations in each case maybe quite significant For example, while solutions containing *spherical* micelles generally exhibit low viscosities, those containing *long rod shaped* micelles frequently exhibit very high viscosities Similarly, cubic phases can display a wide range of stiffness, some samples are as hard as plexiglass, while in others the phases are sufficiently flexible that they almost flow [6]

It is important when considering the use of surfactant phase structures as delivery vehicles to remember that a surfactant aggregate cannot be considered an *inert* carrier, and that the drug and indeed other additives such as preservatives and flavourings* may (depending upon the amount present) dramatically alter the cmc and, in some cases, the type and range of aggregates formed Unfortunately very little work has been performed in this area and is difficult to predict the effect of a drug (or indeed any other additive) on a phase structure as it is expected to vary according to whether the additive (a) is water soluble, (b) adsorbs at the aggregate surface, (c) co-aggregates with the surfactant, or (d) resides in the interior of the aggregate Evidence suggests, however, that the phase structure experiences the most disruption when the additive is itself surface active For example, the presence of the drug lignocaine hydrochloride at concentrations greater than about 5 wt% converts the cubic structure formed from 10 wt% monoolein in water into a lamellar phase [10] The influence of the presence of drug is further complicated because most drugs are administered as salts, hence the amount of amphiphilic salt to lipophilic free drug varies according to pH Consequently the effect of the drug on the phase structure may vary with the pH of the surrounding environment This effect is more likely to be significant if ionic surfactants are used Yet another complication is that if the drug promotes a phase transition, this transition may conceivably be reversed as the release of a surface-active drug from the aggregate proceeds [10] This phase reversal may lead to two different patterns of drug release

* Flavourings are very important if surfactants are to be given orally surfactants do not taste very pleasant Also because of their effect on membranes surfactants may numb the patient s mouth

Table 2 Some physico-chemical properties and potential pharmaceutical applications of surfactant phase structure

Phase Structure	Appearance	Viscosity	Solubilization Capacity	Surfactant Concentration	Possible Use
Micelles	Clear, non-birefringent	Low Least viscous phase	Low amphiphilic and non-polar solutes only	0—25%	Solution for most routes of delivery Protection of labile compounds
Cubic Phase	Clear non-birefringent	Very high Most viscous phase	High amphiphilic and non-polar solutes Low water-soluble solutes	Varies Generally greater than 30%	Viscous preparation for sustained release intramuscular subcutaneous oral and topical Protection of labile compounds
Hexagonal	Clear/cloudy birefringent	Viscous	Probably high amphiphilic and non-polar solutes Low water-soluble solutes	Wide range possible	Sustained release, particularly topical
Lamellar	Clear/Cloudy birefringent	Fairly viscous	Probably high amphiphilic and non-polar solutes Low water-soluble solutes	Wide range possible	Sustained release, particularly topical
Vesicles	Clear/cloudy birefringent	Low viscosity	High amphiphilic and non-polar solutes* Low water-soluble solutes	Fairly low Generally less than 10 wt%	Most routes of administration except oral Protection of labile compounds
Solid	Waxy solid	Stiff	Not known	100 wt%	Solid dispersion for oral use

* The solubilization capacity recorded here refers to vesicles produced by non equilibrium methods those formed spontaneously are expected to exhibit very low capacity for amphiphilic and non polar drugs (see Section 5 4)

4 Choice of Surfactant

Surfactants are well known to exert a wide range of biological, pharmacological, and toxicological effects on man [1] Therefore the single most important factor in the choice of a surfactant, or combination of surfactants, is toxicity Unfortunately this property is hard to assess The reasons for this are many, not the least being the difficulty in finding an appropriate measure of toxicity, especially when screening new surfactants Generally, acute oral toxicological studies are routinely performed on all new surfactants regardless of their intended usage Although this information is valuable it cannot adequately predict chronic toxicity A further complication is the understandable reluctance of the Pharmaceutical Companies to enter into the full scale chronic toxicity studies needed for a proper assessment of a new surfactant for drug delivery purposes, a toxicity study currently costs in the order of 10 million GB pounds Only a very limited number of surfactants are generally considered for formulation purposes Usually only those surfactants are used that have been used in pharmaceutical formulations for many years and are therefore generally recognized as safe, even though some of these surfactants may themselves not have been tested for chronic toxicity[1]

From a toxicological point of view, non-ionic surfactants are generally regarded as the most suitable for pharmaceutical formulation [1 2] Even so the range of non-ionic surfactants used is very limited Tween 80 [polyoxyethylene (20) sorbitan monooleyl ether] and Cremorphor EL [polyoxyethylene (40) castor oil] are probably the two most common There are, however, a large number of non-ionic surfactants commercially available Some of the more common examples are shown in Table 2 A surfactant is composed of three distinct portions a hydrophilic segment, a hydrophobic portion, and a semi-polar linker Consequently it is theoretically possible to join together any combination of segments to produce a surfactant with the required properties, for example biodegradable surfactants can be readily achieved by the use of an ester linkage, while bilayer (vesicle) and micelle forming surfactants can be produced from dialkyl and monoalkyl chain surfactants respectively Despite the wide range of surfactants potentially available, most workers tend to use surfactants that have been previously used in formulation, thereby limiting themselves considerably There is, however, a real need to produce new surfactants in order to realize the full potential of surfactant systems in drug delivery Yet the number of surfactants that can be synthesized is enormous In an attempt to address the problem of design and synthesis of new biocompatible surfactants, a program VESICA[25] has been developed with a view to predicting which potential surfactants would preferentially form a particular aggregate type In this way the number of surfactants that need to be synthesized could be greatly reduced

5 Phase Structures in Drug Delivery

5.1 Normal Micelles

The increased solubility in a micellar solution of an organic substance, insoluble or sparingly soluble in water, is a well established phenomenon Indeed the solubilization of water-insoluble drugs by micelles has long been investigated as a means of improving solubility for drug delivery, in particular for parenteral or oral administration, but also for ophthalmic, topical, rectal, and nasal delivery [1 2] The protection of labile drugs from the environment through solubilization within micelles has also been examined Consequently an enormous number of papers examine the incorporation of a wide variety of drugs into micelles formed from a large variety of surfactants, and in particular non-ionic surfactants of the type shown in Table 3 [1 2] There are, however, only a few products on the market that can be considered to be micellar systems This is mainly because solubilization capacity is usually too low to be of practical use, with only a few mg of drug solubilized per g of surfactant As the average dose of a drug is in the order of tens of mg and, as the concentration of the micellar solution is never more than 20 wt% surfactant, this means that solubilization is not feasible except in a few instances where very potent lipophilic drugs, *e g* testosterone, are incorporated

Attempts have been made to design non-ionic surfactants with an improved solubilization capacity An early approach involved the production of larger micelles Despite an increased micelle size, solubilization decreased upon lengthening the hydrophobic chain, this decrease was attributed to deleterious

Table 3 Commonly encountered non-ionic surfactants

Hydrophilic Group	Hydrophobic Group	Linker Moeity	Common Name
Polyoxyethylene	Cholesterol	Ether	Solulan
	Long chain alcohol	Ether	Brij
	Long chain acid	Ester	Myrij
	Long chain acid	Sorbitan ring	Tween
	Alkyl phenol	Ether	Triton
	Alkyl amide	Amide	-----
	Alkyl amine	Amine	-----
	Polyoxypropylene	Ether	Pluronic
	Long chain triglycerides	Ester	-----
Sugar	Long chain alcohol	Ether	-----
	Long chain acid	Ester	-----
Sorbitan ring	Long chain acid	Ester	Span
Crown ether	Long chain acid	Ether	-----
Tertiary amine oxide	Long alkyl chain	-----	-----

changes in the polyoxyethylene chains nearest to the core, the main locus of solubilization for most drugs [26] As the amount of drug solubilized in the core is usually less than a few percent of the total drug incorporated in the micelle, the same group attempted to promote solubilization in this region by the introduction of a semi-polar group into the hydrophobic chain Incorporating a single ether linkage in the hydrophobe resulted in a marked reduction in the tendency to aggregate and, as a consequence, a significant reduction in solubilization [27] This modification was obviously counter-productive and suggests that solubilization cannot be improved by altering the nature of the hydrophobic region and that it may be better to consider replacing the usual polyoxyethylene head group Data do suggest that it may be feasible to achieve significant increases in solubilization by using alternative head groups such as the amine oxides [28]

Even if it is possible to increase solubilization to a sufficient degree (ideally to about a 100 mg per g of surfactant) there are still a number of problems with the use of micellar solutions for drug delivery One of the major problems is the large dilution the system experiences upon administration This dilution is particularly large after oral and intravenous administration, and can cause the unwanted precipitation of drug In the case of oral delivery this may lead to irritation of the gastrointestinal tract, while in the case of intravenous administration, pain may be experienced upon injection

Other complicating factors experienced when using micellar solutions include the concomitant solubilization of other additives such as preservatives and sweetening agents, some surfactants taste foul, especially if administered as a solution Depending upon their relative sites of incorporation in the micelles this co-solubilization can either lead to a decrease or increase in drug solubilization [1] This potential problem of concomitant solubilization of additives is not just limited to micellar systems and is encountered with all surfactant systems

Owing to their labile nature, micelles can only be used as drug carriers and not as targetting systems, although there is a small amount of evidence that suggests it may be possible to alter the biodistribution of a drug by administering it in a micellar solution [29] This alteration has, however, been attributed (at least in part) to a direct effect of the surfactant (in this case, the non-ionic surfactant Tween 80) on biomembrane permeability, most micelle-forming surfactants are known to influence the permeability of biomembranes [1 2] Furthermore, as most of the surfactants used for drug delivery are not readily biodegradable, their activity is retained for long periods in the body

Although drug solubilization in micelles has been extensively investigated, much less work has been performed examining the influence on drug transfer of solubilization in micelles According to the limited evidence available, micellar solubilization reduces the rate of mass transfer of most drugs across inert membranes [1 2] In the body this effect appears to be counterbalanced by the fact that the surfactant can frequently increase membrane permeability

5.2 Cubic Phases

Cubic phases have received a considerable amount of attention as putative drug delivery systems [10 23 30—35] One interesting cubic phase is that formed by the polyoxyethylene–polyoxypropylene co-block polymer, pluronic F127 This particularly attractive system has a high solubilizing capacity and is generally considered to be relatively non-toxic In aqueous solution, at concentrations greater than 20 wt%, F127 is transformed upon heating from a low viscosity transparent (micellar) solution at room temperature to a solid clear gel (cubic phase) at body temperature Other members of the pluronic series also undergo a liquid to gel transformation at around body temperature, but only at higher surfactant concentrations (namely 30 wt% and above) [33] This thermal gelation, which is reversible upon cooling, has a number of important applications in drug delivery For example, a solution poured onto the skin or injected into the body will gel to form a solid sustained release depot Furthermore, since the gelation is reversible, removal from the skin is facilitated by simply immersing, or irrigating the skin with cool water Removal from a body cavity is more difficult, however, and would require a surgical procedure In order to circumvent this problem some workers are currently trying to synthesize biodegradable surfactants that will undergo a thermal reversible gelation at a similar temperature to that of F127 [34]

To date the cubic phase of F127 has been investigated for a wide range of applications including topical delivery, covering of burn wounds, ophthalmic delivery, rectal delivery, as a vehicle for injectables by both intramuscular and subcutaneous routes, and as a bioadhesive [30 33] Drug release from the cubic phase is governed by the physico-chemical properties of the solute and the concentration of the surfactant [30 31] As a general rule increasing solute lipophilicity and/or increasing surfactant concentration leads to a decrease in release rate As a consequence the cubic phase of F127 has considerable potential as a sustained release preparation

Another cubic phase undergoing extensive studies for pharmaceutical purposes is that formed by monoolein and water [10 23 32] A great advantage to the use of monoolein is that it is subject to enzymatic lipolysis in a wide range of tissues and is therefore considered to be biodegradable With respect to drug delivery the most interesting property of the cubic phase formed by monoolein is its ability to co-exist with water at body temperature As a consequence it is possible to formulate a system so that when added to water it does not undergo a phase change None of the other long chain monoglycerides, with the exception of monoerucin and sunflower oil monoglycerides, have been reported to form a cubic phase over a temperature range suitable for exploitation in drug delivery [6]

The cubic phase of monoolein occurring at about 50—60 wt% monoolein has been shown to incorporate, at levels up to 5—10 wt%, a large range of drugs of very different size and polarity, including a number of proteins and oligopeptides, without experiencing a phase change [32] At higher levels of incorporated drug, depending upon the nature of the drug, phase changes may be observed The reason proposed for the ability of the cubic phase to solubilize such a wide range of drugs is its very large interfacial area – in the order of 400 m^2/g cubic phase [32]

As with F127 the cubic phase of monoolein has been shown to extend significantly the release of bioactive substances both *in vitro* and *in vivo* [32] Again, in agreement with F127, the pattern and rate of release will be very dependent upon the nature of the drug The cubic phase also has the advantage of being able to reduce the enzymatic degradation of the incorporated proteins and peptides, possibly because the enzyme has restricted access to the substrate [32] The cubic phase of monoolein has been

proposed as a vehicle for drug uptake from the gastrointestinal tract or as a subcutaneous or intramuscular depot for sustained release, although in the latter examples, because of the viscosity of the phase, discomfort would be experienced upon injection Discomfort can be overcome, however, by formulating the monoolein to undergo a phase transition to the cubic phase on injection This phase transition can be achieved in one of two ways (i) by exploiting the transformation from a relatively low-viscosity lamellar phase at room temperature to the stiffer cubic phase present at body temperature, (ii) by utilization of the transition from a lamellar phase to a cubic phase upon addition of water [23] Formulating monoolein in either manner creates a precursor that is easily handled and can be injected without causing distress [23] The use of monoolein in combination with other surfactants, for example the non-ionic surfactant polyoxyethylene (20) oleyl ether (Brij 96), has also been studied in order to promote favourable phase transitions [23]

One property of the cubic phase of monoolein that does not seem to have been exploited yet is its bioadhesive properties (it appears that most cubic phases are bioadhesive) As a result of these properties the cubic phase could have some use in rectal and vaginal delivery

5 2 1 Cubosomes

The cubic phase has been dispersed by homogenization with the aid of F127 and lecithin to produce so-called cubosomes [10] Cubosomes have a particle size distribution similar to that found in commercially available oil-in-water emulsions intended for parenteral nutrition The 'cubic phase emulsion' contains water and it is hoped that this will extend drug release *in vivo*

To date the only cubic phases that have been investigated for their use as drug delivery systems are those formed by F127 and monoolein Yet cubic phases are commonly found in a wide variety of surfactant systems [6] Many of these cubic phases may have a place in drug delivery – and since they can be found in non-aqueous polar solvents such as ethylene glycol, and since such solvents frequently exhibit a higher capacity than water for many hydrophilic drugs, the possibility exists to increase the loading of some cubic phases

5.3 Liquid Crystalline Phases

Liquid crystalline lamellar phase structures are currently recognized as important in pharmaceutical formulation Hydrophilic creams are oil-in-water mixtures stabilized by lamellar structures and it has been suggested that the lamellar structures within hydrophilic creams are sometimes the factor controlling release of drug from the system To date very little work has examined the possibility of using lamellar phases or indeed hexagonal phases for drug delivery Yet a large number of surfactants, particularly those formed from non-ionic surfactants, form liquid crystalline phases over a wide range of surfactant concentrations In addition most of the work that has been performed examining the use of liquid crystalline phases in drug delivery has not bothered to characterize the nature of the phase structure, that is, whether the liquid crystalline phase is hexagonal or lamellar in nature, yet it is known that the release pattern differs depending upon the phase structure present [35]

5 3 1 Lamellar Phases

Only a small amount of work reported in the literature specifically examines the use of lamellar phases Yet lamellar phase structures exhibit interesting solubility properties, in the lamellar structure lipophilic bilayers alternate with hydrophilic layers which contain interlamellar water, hence it is possible to incorporate water-soluble, oil-soluble, and amphiphilic drugs Furthermore evidence suggests that some drugs are more soluble in the liquid crystalline lamellar phase than in isotropic liquids of similar composition [24]

Generally a drug permeating through a lamellar gel network may follow an interlamellar or translamellar route, depending on local rates of diffusion and partition Extremely lipophilic drugs will probably be trapped inside the lipophilic bilayers,[24] while extremely hydrophilic drugs will permeate through the hydrophilic regions between the lamellae, and amphiphilic drugs may move both between and across the lamellae [36] In the latter case interesting release patterns have been predicted theoretically [36] For extremely hydrophilic drugs the interlamellar aqueous channels behave as pores, the tortuosity of which is determined by the amount of free water and the orientation of the lamellae [36] The diffusion coefficient of a drug within a lamellar phase is about one to two orders of magnitude smaller than that in solution [37] As a result of their control over drug release, it has been suggested that liquid crystalline phases and in particular lamellar phases are potentially very useful systems for the topical delivery of drugs [24] In addition, if the release rate from the surfactant system is less than the diffusion of the drug through the skin then the surfactant system can be used as a topical controlled-release preparation One potential problem with topical application of lamellar phases is that dehydration of the skin may occur, resulting in irritation

Reverse micelles containing drug and lecithin in oil have recently been investigated as a precursor to a sustained release lamellar phase formulation [38] By clever formulation it should be possible to produce a reverse micellar solution of drug which transforms into a liquid crystalline system on contact with biofluids The feasibility of such an approach has been demonstrated *in vitro* using an oily solution containing reverse micelles consisting of phospholipid and drug On contact with aqueous media this solution was shown to change its microstructure from spherical or cylindrical micelles to lamellar liquid crystals As the diffusion was smaller by a factor of 100 in the lamellar phase compared to the oily solution, the formulation has potential as a sustained-release preparation for intramuscular or subcutaneous administration Further, as the diffusion of the drug was also dependent upon the thickness of the liquid crystalline layer which was in turn influenced by whether free acid or base was solubilized in the system, it may be possible to achieve a fine tuning of release properties

5.4 Helical Bilayers

These more unusual phase structures have recently been investigated as a drug delivery vehicle [39] The core of these tubular-like structures has been filled with a polymer matrix containing drug in an attempt to produce a sustained-release formulation, animal studies showed that slow release of drugs occurred for up to 5 days

5.5 Vesicles

Since the realization in the seventies that phospholipid vesicles (or liposomes) had potential as drug delivery systems, vesicles have probably been the most extensively investigated of all surfactant systems Vesicles (niosomes) produced from non-ionic surfactants have also been widely studied [4 40] Their higher chemical stability, better chemical definition, and reduced cost mean that niosomes have a number of advantages over liposomes [4]

As vesicles are generally non-equilibrium structures a large number of different types of vesicles can be produced [11] The nature of the preparation of the vesicle can determine its physical stability,[4] an important consideration when using vesicles for drug delivery In addition, the choice of vesicle type also depends both on the nature of the drug to be encapsulated and on the desired route of administration The type of vesicle is critically important only for hydrophilic drugs as different vesicle types can encapsulate different amounts of aqueous phase and consequently different amounts of water-soluble drug Lipid-soluble drugs are readily entrapped in the hydrophobic bilayer structure and as a consequence are less sensitive to vesicle type One advantage of using vesicles formed by non-equilibrium methods is that they are not normally broken down

upon dilution They are, however, liable to destruction in the presence of biological surfactants such as the bile salts and lysolecithin

The main route of administration of vesicles is by intravenous injection Unfortunately most vesicles are removed rapidly from the systemic circulation by the fixed macrophages of the liver However, by clever manipulation of the formulation, for example by coating phospholipid vesicles with a hydrophilic polymer such as polyoxyethylene glycol, uptake by the liver can be reduced, thereby retaining the vesicles in the circulation for longer periods and allowing them to act as sustained release vehicles By incorporating targetting ligands on the surface of such vesicles it then becomes feasible to direct the vesicles to certain organs and deposit them there This well-established approach using liposomes, has not yet been investigated using niosomes Other routes of administration that have been examined using niosomes include the topical route [41] In addition the nasal, occular, oral, rectal, and pulmonary routes have all been extensively examined using vesicles prepared from phospholipids

To date no work has been reported investigating the potential of spontaneously formed vesicles for drug delivery One reason is that the only biocompatible surfactant producing these vesicles, GM3, is prohibitively expensive Also, with this type of vesicle, entrapment of non-polar or amphiphilic drugs will probably be difficult Another problem with using spontaneously formed vesicles is that they are very small and as a consequence would be expected to exhibit a very low capacity for water-soluble drugs One advantage of this very small size, however, is that the vesicles would probably avoid uptake by the fixed macrophages of the liver Another advantage would be their improved stability

A patent has been published claiming a wide range of pharmaceutical uses for the recently discovered reverse vesicle, these applications include the topical, nasal, rectal, and parenteral routes of administration [42] Reverse vesicles have the potential to protect sensitive compounds from the environment

5.6 Reverse Micelles

A possible exploitation of the association of surfactant in non-polar media is the production of reverse micellar solutions containing drug for use in the production of therapeutic aerosols from pressurized metered dose inhalers These are currently the major devices used in the delivery of drugs to the respiratory tract This situation is unlikely to change in the near future, although fluorinated gases will replace the currently used chlorofluorocarbon propellants To date only one study has been performed and although this study examined the use of phospholipids, rather than non-ionic surfactants, it did demonstrate the concept [43] The work showed that the level of drug delivered *in vitro* from the reverse micellar solution was comparable with that obtained from the commercially available suspension formulation For hydrophilic drugs the loading achievable in reverse micelles is limited by the amount of water solubilized in the core of the aggregate, it may be possible to improve this incorporation by replacing water with a non-aqueous polar solvent, such as glycerol or polyoxyethylene glycol Other potential applications of reverse micelles include the protection of labile drugs *via* the oral, subcutaneous, and intramuscular routes However, these possibilities remain as yet untried

5.7 Solid Surfactant

One serious problem facing the pharmaceutical scientist is the formulation of poorly water-soluble drugs Frequently the oral bioavailability of such drugs is very poor as a result of their slow dissolution in the aqueous medium of the gastrointestinal tract It is difficult to find water-soluble excipients that completely dissolve the active ingredients after addition of water, that maintain the drug in solution for long periods even upon dilution, do not impair absorption, and are non-toxic In an attempt to solve these problems one group has examined the production of a solid solution of drug (cyclosporin) and non-toxic surfactant (sugar esters) [44] The loading of the poorly-soluble drug used was about 14 wt% The solid solution readily dissolves in the contents of the small intestine to form a clear micellar solution of solubilizate Presenting a drug in this way should overcome some of the problems inherent when using micellar formulations Furthermore as the solution is solid it should be relatively easy to enclose the drug within a capsule, although as the formulation is hygroscopic care will be needed when storing the capsules An added advantage is the possibility of directly compressing the solid solution to form tablets Unfortunately, while the method has significant benefits, it is limited to surfactants that are solid at room temperature, although a solid solution can be produced from a liquid surfactant such as Tween 80 through admixture of a polymer such as polyoxyethylene glycol [45] The technique is also limited to drugs that are readily soluble in the micellar solution formed from the surfactant in the small intestine

6 Conclusion

A number of equilibrium surfactant structures and related systems have considerable potential as delivery systems for a wide range of drugs Some of the more unusual aggregates such as fibre gels have no obvious use in pharmacy at the moment, but may prove to be exploitable in the near future Most surfactant systems, with the exception of ligand modified vesicles, have little potential as targetting devices Before attempting to formulate a drug the limitations of each type of system need to be thoroughly understood For example, it is no use trying to increase the aqueous solubility of a water-soluble hydrophilic drug in an aqueous-based surfactant system However, it may be beneficial to formulate a hydrophilic drug in a surfactant system if a protective effect or a sustained release is required Similarly it would be of little advantage formulating a drug requiring a very high dose in a micellar solution

The most serious problem with formulating drugs in surfactant systems is the paucity of suitable, biodegradable surfactants commercially available Until this situation is rectified surfactants will not live up to their full potential as delivery vehicles and possibly as targetting systems With all the current interest in the area there is hope that this situation will at least in part be rectified in the near future

7 References

1 D Attwood and A T Florence, 'Surfactant Systems Their Chemistry, Pharmacy and Biology', Chapman and Hall, London, 1983
2 A T Florence, 'Techniques of Solubilization of Drugs', ed S H Yalkowsky, Marcel Dekker, Inc , New York, 1981
3 E Tomlinson, in 'Site-specific Drug Delivery', ed E Tomlinson, John Wiley and Sons Ltd , Chichester, 1986
4 A Y Ozer, A A Hincal, and J A Bouwstra, *Eur J Pharm Biopharm* , 1991, **37**, 75
5 J Israelachvili, 'Intermolecular and Surface Forces' 2nd Edition, Academic Press, London, 1991
6 K Fontell, *Colloid Polym Sci* , 1990, **268**, 264
7 D J Mitchell, G J T Tiddy, L Waring, T Bostock, and M P McDonald, *J Chem Soc Faraday Trans 1*, 1983, **79**, 975
8 A S Rudolph, J M Calvert, M E Ayers, and J M Schnur, *J Am Chem Soc* , 1989, **111**, 8516
9 J -H Fuhrop, S Svenson, C Boettcher, E Rossler, and H -M Vieth, *J Am Chem Soc* , 1990, **112**, 4307
10 S Engstrom and L Engstrom, *Int J Pharm* , 1992, **79**, 113
11 M J Lawrence, in 'Controlled Particle, Droplet and Bubble Formation', ed D J Wedlock, Butterworth-Heinemann, Oxford, 1994
12 H Kunieda, K Nakamura, and D F Evans, *J Am Chem Soc* , 1991, **113**, 1051
13 M Corti, L Cantu, and P Salina, *Adv Colloid Interface Sci* , 1991, **36**, 153
14 H Kunieda, K Nakamura, U Olsson, and B Lindman, *J Phys Chem* , 1993, **97**, 9525
15 D Cochin, F Candu, and R Zana, *Macromolecules*, 1993, **26**, 5755

16 P Strom, *J Colloid Interface Sci*, 1992, **154**, 184
17 J H Fendler and P Tundo, *Acc Chem Res*, 1984, **17**, 3
18 W J Bailey and L -L Zhou, *ACS Symp Ser*, 1991, **469**, 285
19 M O Vaizoglu and P P Speiser, *Acta Pharm Suec*, 1986, **23**, 163
20 M Yokoyama, M Miyauchi, N Yamada, T Okano, Y Sakurai, K Kataoka, and S Inoue, *J Control Rel*, 1990, **11**, 269
21 S A Charman, W N Charman, M C Rogge, T D Wilson, F J Dutko, and C W Pouton, *Pharm Res*, 1992, **9**, 87
22 T Yoshioka and A T Florence, *Int J Pharm*, *Int J -Pharm*, 1994, **108**, 117
23 S Engstrom, L Lindahl, R Wallin, and J Engblom, *Int J Pharm*, 1992, **86**, 137
24 S Wahlgren, A L Lindstrom, and S E Friberg, *J Pharm Sci*, 1984, **73**, 1484
25 S M Lawrence, M J Lawrence, and D J Barlow, *J Mol Graphics*, 1991, **9**, 218
26 P H Elworthy and M S Patel, *J Pharm Pharmacol*, 1982, **34**, 543
27 D Attwood, P H Elworthy, and M J Lawrence, *J Pharm Pharmacol*, 1989, **41**, 585
28 M J Lawrence and F Devinsky, *J Pharm Pharmacol*, 1988, **40**, 125P
29 M N Azmin, A T Florence, R M Handjani-Vila, J F B Stuart, G Vanlerberghe, and J S Whittaker, *J Pharm Pharmaocol*, 1985, **37**, 237
30 J C Gilbert, J Hadgraft, A Bye, and G Brookes, *Int J Pharm*, 1986, **32**, 223
31 P -C Chen-Chow and S G Frank, *Int J Pharm*, 1981, **8**, 89
32 B Ericsson, P O Erikson, J E Lofroth, and S Engstrom, *ACS Symp Ser*, 1991, **469**, 251
33 S Miyazaki, C Yokouchi, T Nakamura, N Hashiguchi, W -M Hou, and M Takada, *Chem Pharm Bull*, 1986, **34**, 1801
34 L Martini, D Attwood, J H Collett, C V Nicholas, S Tanodekaew, N -J Deng, F Heatley, and C Booth, *J Chem Soc Faraday Trans*, 1994, **90**, 1961
35 H G Ibrahim, *J Pharm Sci*, 1989, **78**, 683
36 H E Bodde, T De Vringer, and H E Junginger, *Progr Colloid Polymer Sci*, 1986, **72**, 37
37 C C Mueller-Goymann and S G Frank, *Int J Pharm*, 1986, **29**, 147
38 C C Mueller-Goymann and H -J Hamann, *J Control Rel*, 1993, **23**, 165
39 F R Service, *Science*, 1994, **252**, 316
40 H E J Hofland, J A Bouwstra, G S Gooris, F Spies, H Talsma, and H E Junginger, *J Colloid Interface Sci*, 1993, **161**, 366
41 H E J Hofland, J A Bouwstra, M Ponec, H E Bodde, F Spies, J Coos Verhoef, and H E Junginger, *J Control Rel*, 1991, **16**, 155
42 Patent application A61K9/127
43 R E Evans and S J Farr, *J Biopharm Sci*, 1992, **3**, 33
44 L Hahn and H Sucker, *Pharm Res*, 1989, **6**, 958
45 K R Morris, G T Knipp, and A T M Serajuddin, *J Pharm Sci*, 1992, **81**, 1185