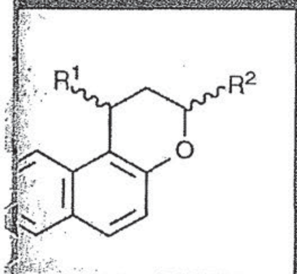
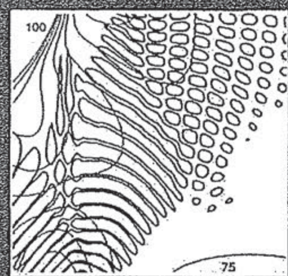
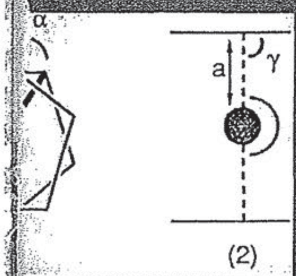
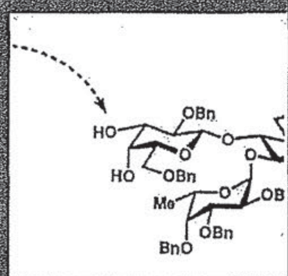
CHEMICAL SOCIETY
REVIEWS

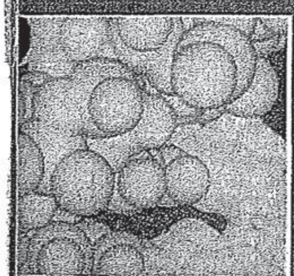
Volume 23 Issue 6 Pages 363–442 December 1994

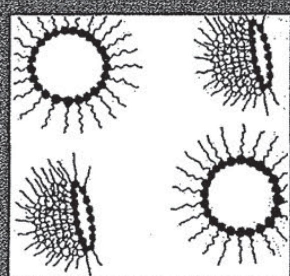


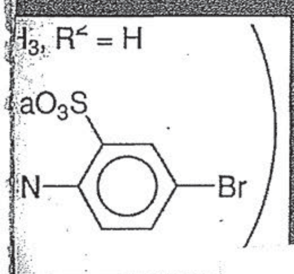


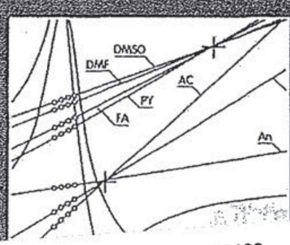












ISSN 0306-0012

It is intended that **Chemical Society Reviews** will have the broad appeal necessary for researchers to benefit from an awareness of advances in areas outside their own specialities. Deliberate efforts will be made to solicit authors and articles from Europe which present a truly international outlook on the major advances in a wide range of chemical areas. It is hoped that it will be particularly stimulating and instructive for students planning a career in research. The articles will be succinct and authoritative overviews of timely topics in modern chemistry.

In line with the above, review articles will not be overly comprehensive, detailed, or heavily referenced (*ca.* 30 references), but should act as a springboard to further reading. In general, authors, who will be recognized experts in their fields, will be asked to place any of their own work in the wider context. Review articles must be *short*, around 8–10 journal pages in extent. In consequence, manuscripts should not exceed 20–30 A4/American quarto sheets, this length to include text (in double line spacing), tables, references, and artwork. An Information to Authors leaflet is available from the Senior Editor (Reviews).

Although the majority of articles are intended to be specially commissioned, the Society always considers offers of articles for publication. In such cases a short synopsis (including a selection of the literature references that will be cited in the review and a brief academic CV of the author), rather than the completed article, should be submitted to the Senior Editor (Reviews), Books and Reviews Department, The Royal Society of Chemistry, Thomas Graham House, Science Park, Milton Road, Cambridge CB4 4WF.

Typeset by Servis Filmsetting Ltd.
Printed in Great Britain by

Surfactant Systems: Their Use in Drug Delivery

M. Jayne Lawrence
Department of Pharmacy, King's College London, University of London, Manresa Road, London SW3 6LX

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]

M. Jayne Lawrence graduated in Pharmacy from Liverpool Polytechnic (B.Sc.) in 1981 and qualified as a member of the Royal Pharmaceutical Society of Great Britain in 1982. She received her Ph.D. degree in 1985 from the University of Manchester. Since 1984 she has been a Lecturer in the Pharmacy Department, King's College London. Her research interests cover the design, synthesis, and physio-chemical characterization of surfactant systems and membrane transport.

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

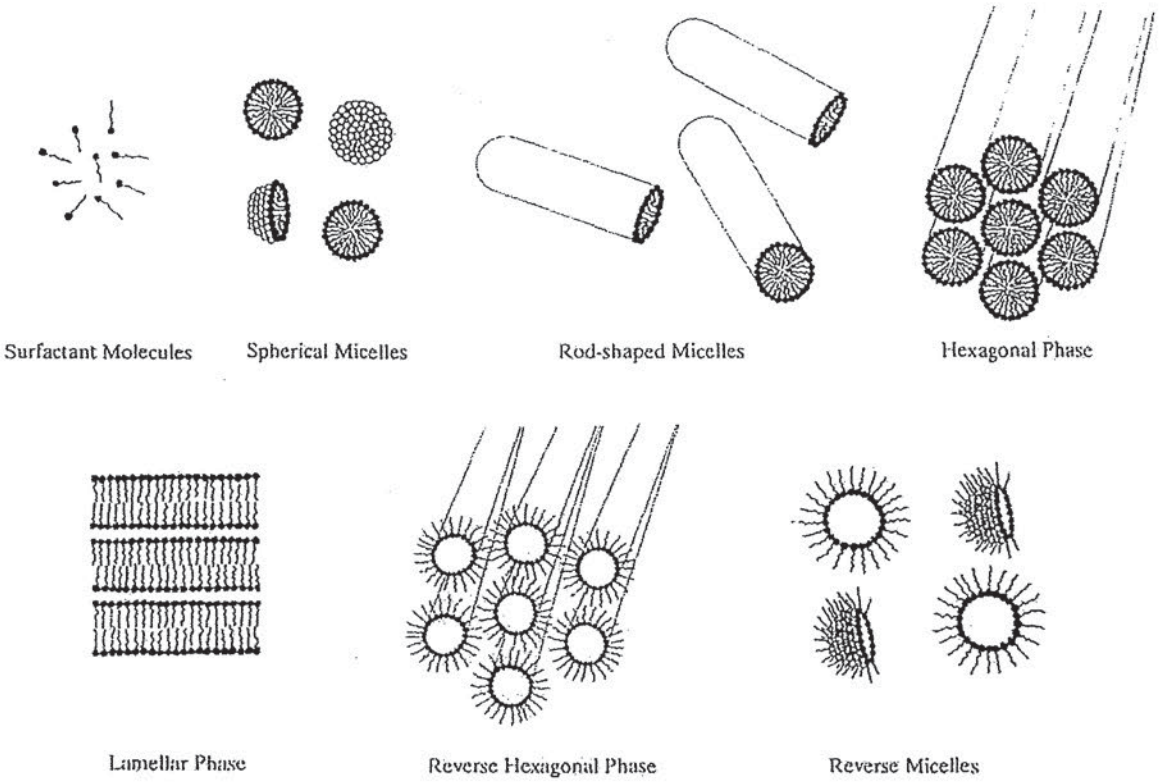


Figure 1

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.

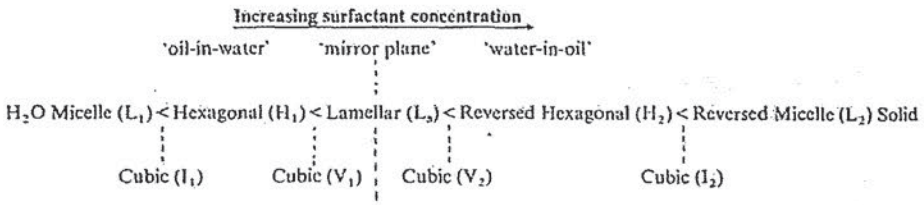


Figure 2 Idealized phase sequence in surfactant–water systems. (Modified from reference 6; terminology as in reference 7.)

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 physico-chemical 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.

DOCKET ALARM

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts

Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research

With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips

Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS
Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS
Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS
Sync your system to PACER to automate legal marketing.