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# The Increasingly Clever Micelle*

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Science is much more than a mere body of facts; it is a collection of data from experiments and observations, the collection having been assembled according to the collector's interests and points of view.[1] Because of this definition, I intend to present in this lecture my personal view of micellisation, and it should be clear that I have excluded much material. Pharmacy is a tapestry woven from the threads of different sciences. I choose my thread, which is the physical chemistry of surfactants, and proceed to weave it into a fuller pharmaceutical picture.

Micellisation is a phenomenon given by surfactants, which I use as an overall name for soaps, detergents and surface active agents. These materials have been in use from primitive times for purposes such as pudding clay. The characteristic feature of surfactants is that they have two distinct regions in their molecular structure; one region is hydrophobic and does not want to mix with water, the other is hydrophilic and likes being in an aqueous environment. In sodium dodecyl sulphate there is a 12-carbon chain linked to a sulphate group (Fig. 1). In hexadecyl-trimethylammonium bromide a 16-carbon chain is linked to a quaternary ammonium head group. These are anionic and cationic surfactants respectively, classified on the basis of the charge carried by the long chain ion. A nonionic surfactant contains a polyoxyethylene chain as its hydrophilic group. The fourth class of surfactants is loosely termed naturally occurring; an example is lecithin in which two hydrocarbon chains are linked to a glycerol residue, which has a phosphatidyl-choline head group.

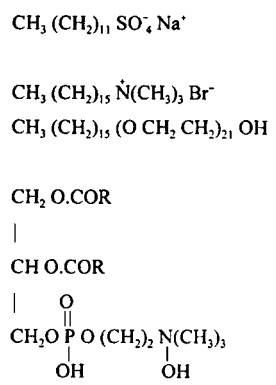

Fig. 1: Structures of surfactants. From top of figure to bottom; sodium dodecyl sulphate, hexadecyltrimethyl-ammonium bromide, a non ionic surfactant, and a naturally occurring surfactant and, lecithin.

In solution these compounds form a micellar structure with the hydrocarbon chains inside the micelle and the polar groups on the outside. In ionised surfactants some of the counterions are bound to the micelle.

In 1913 James McBain[2] recognised that soaps micellised in aqueous solution. A few years later Lt. Col. Harrison started his technical innovations on gas masks in the 1914–18 war. Also in 1913 there was a Faraday Society Discussion at which papers were presented by such giants of colloid science as Ostwald, Freundlich and Hatschek. Pauli presented a paper on the viscosity and electrochemistry of protein solutions, and expressed

*An edited version of the Harrison Memorial lecture delivered in London on December 1 1976 and reproduced with permission from the *Pharmaceutical Journal* 1976, 217: 566–580

difficulty at correlating the high viscosity of protein solutions with their high conductance, because a high viscosity is expected to reduce electrical conduction. McBain took part in the discussion using the words 'highly charged colloidal aggregates'. He assumed excessive hydration of the colloidal particle in order to explain why it should be so mobile in an environment that was so viscous. He saw difficulties in applying the explanation to soaps 'without making very daring further assumptions'. He said: 'This contradiction between the results of conductivity and of osmotic pressure would seem to be one of the most important colloidal problems awaiting definite solutions'. He was indeed correct.

McBain's experimental evidence, presented verbally at that meeting in 1913 was this: a Normal solution of sodium palmitate has a conductance comparable with one of sodium acetate but its rise in boiling point is only a quarter as great as that of a Normal solution of sodium acetate. As the rise in boiling point is inversely proportional to the molecular weight of the species in solution, that meant that the sodium palmitate formed a large structure, but that it still conducted electricity. He therefore postulated the formation of a highly charged colloidal aggregate. Although wrong in some details, McBain's general idea was correct, and much that has happened in this field in the past 63 years stems from it. Why do micelles form, and have the structure that they do? If the concentration of the surfactant in water is increased from zero, the surface tension of the solution decreases, and then becomes roughly constant.

The conductivity does not change much at low concentrations, but falls at higher ones. Most physical properties of the solution change at this point, which is called the critical micelle concentration (CMC). Adsorption of the surfactant at the air/water interface causes the surface tension to fall below the CMC, so that if the solution is shaken it will foam. Why then, do surfactant molecules go to the surface, or into micelles: the reasons for both transitions are fundamentally the same[3]. When a single surfactant molecule is moved into an interfacial film or into a micelle (Fig. 2), the polar head groups are forced close together and work must be expended to do this, just as hard work is needed to force together the like poles of two magnets.

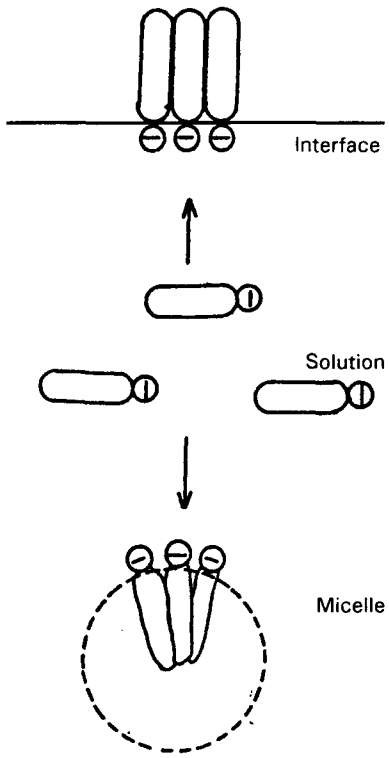


Fig. 2: Transfer of surfactant into an interface or a micelle.

However, two other factors provide a lowering of the free energy of the system, which more than offsets the free energy rise from the electrical work, and as all chemical systems tend towards the lowest possible energy state, transfer of the molecules to the interface or into the micelle is favoured. One of the factors is that the high interfacial energy between the hydrocarbon chain and water is lost when the chain is placed in contact with others in the surface or in the micelle. The other factor is more complex. Water molecules close to the surfactant monomer are more ordered than liquid water itself; this degree of order is lost when the monomer is placed in the micelle (Fig. 3).

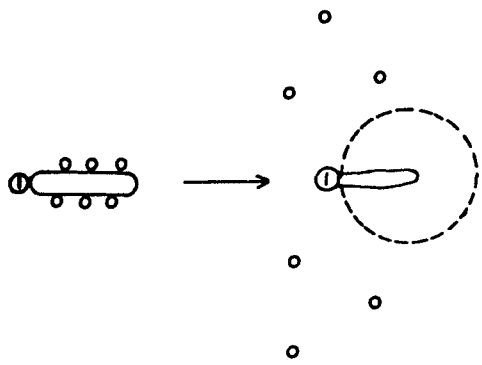

Fig. 3: Loss of water structure from surfactant monomer when transferred to a micelle.

This gives a positive entropy change, and the free energy is lowered because:

$$\Delta G \propto T\Delta S$$

where G = free energy and S = entropy. For some years it has been considered that the disorder on micellisation arose from water molecules which had formed a hydrogen bonded structure around the hydrocarbon chain of free surfactant monomers, becoming disordered when these monomers were placed in the micelle. Howarth[4] has re-examined hydrophobic bonding, and suggests that the water molecules in fact restrain the motions of the hydrophobic parts of the solute. On placing them in the micelle they have increased freedom, giving the order to disorder change.

The overall result as concentration is increased, is that adsorption at the surface takes place, which helps to lower the free energy of the system. When this mechanism for lowering the free energy is exhausted, micellisation takes place. Much of micellar behaviour can be predicted from these energy changes.

**Factors affecting micellisation**

Starting with an average micelle (Fig. 4), note that 70 to 80 per cent of counterions are bound to the micelle and that the interior is liquid in nature. As a rough approximation, altering the nature of the ionised head groups does not alter the micelle size or the CMC to a great degree. The micelle size is decreased and the CMC occurs at higher concentrations by increasing the polyoxyethylene chain length in a non-ionic surfactant which makes

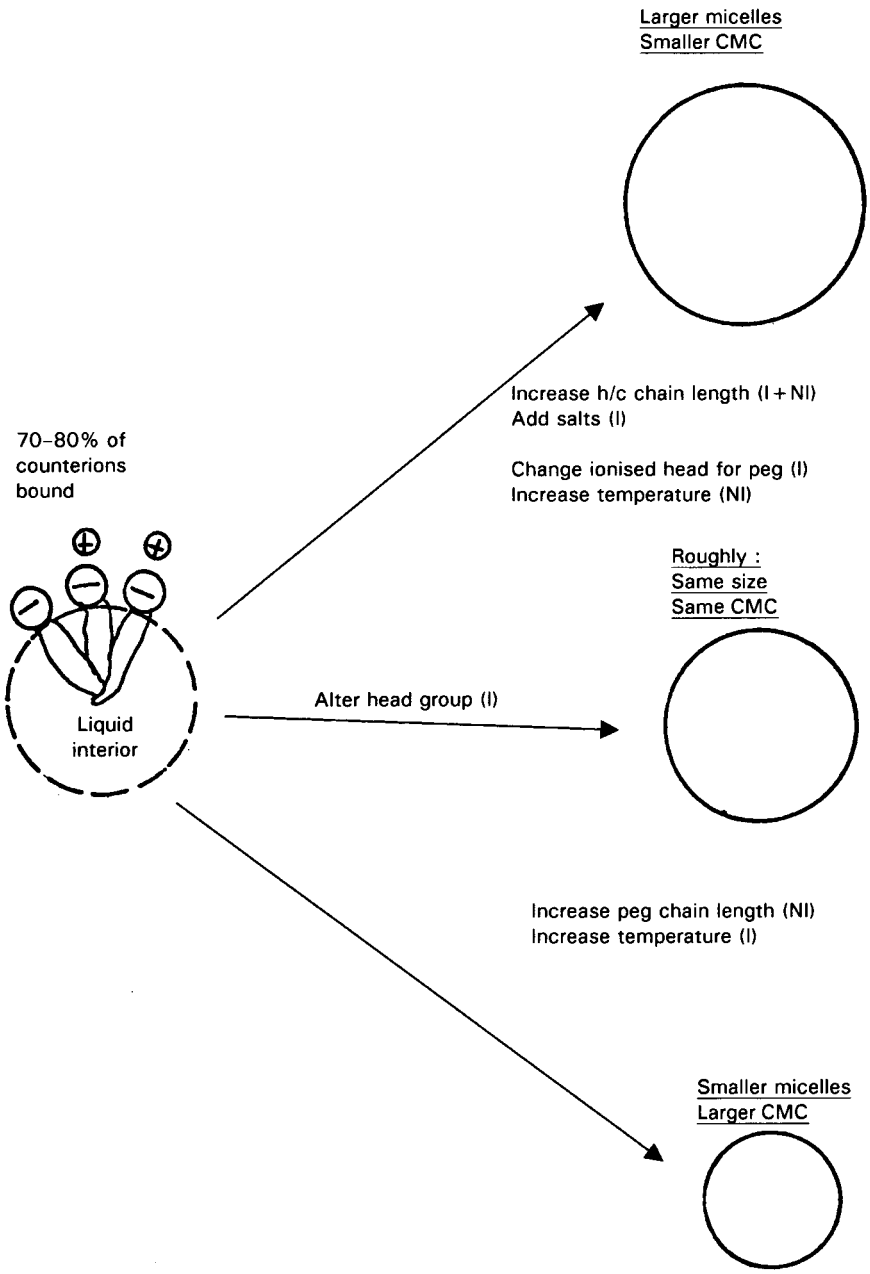


Fig. 4: Some factors affecting micellisation. NI = non ionic, I = ionic, h/c = hydrocarbon, peg = polyethylene glycol.

the monomer more hydrophilic and less likely to micellise, or by increasing the temperature which breaks up ionic micelles because of additional thermal agitation at high temperatures. To obtain bigger micelles forming more readily at lower concentrations: (a) increasing the hydrocarbon chain length increases the driving forces causing micellisation which are associated with the hydrocarbon chain, (b) adding neutral salts to ionised surfactants decreases the work needed to force the polar heads together, (c) changing an ionised head group to a polyoxyethylene chain for the same reason as (b), (d) increasing the temperature in the case of nonionic surfactants (for reasons which are not completely understood). Nearly all the above changes can be deduced from the energy changes discussed earlier.

It has been implied that micelles are spherical in shape[3] , and this is approximately true in dilute solutions, but at high concentrations asymmetrical particles are present. Micelles are also hydrated, and the non-ionic type

can be heavily hydrated. The polyoxyethylene structure provides space for mechanical trapping of water molecules as well as for hydrogen bonding. Micelles are not rigid spheres, but exist in a state of dynamic equilibrium. There are now many results reported for the rate constants of micelle formation and dissociation[5].

As the concentration of the surfactant is increased, monomers are present in solution until the CMC is reached (Fig. 5).

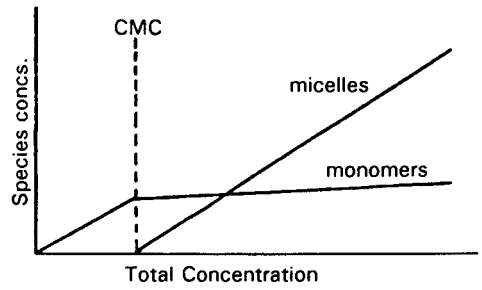


Fig. 5: Variation of species concentrations in the CMC region.

Thereafter nearly all the solute added to the solution forms into micelles, at least from micelles containing 20 or more monomers. The monomer concentration only increases slightly above the CMC. However, it is possible to detect this increase, which is important in knowing which theoretical treatment to use to represent the micellisation process[5].

## Applications of surfactants

Uses of surfactants can, for convenience, be divided into two classes: (a) arising from adsorption at interfaces – wetting, detergency, emulsification, suspension stabilisation, aerosol formulation, penetration into powder beds, and ore flotation; (b) arising from the presence of micelles – solubilisation, the presentation of insoluble drugs, liposomes, micellar catalysis, levelling of dyes, interaction with preservatives, non aqueous gels, and emulsion polymerisation.

There are other applications, but the list is long enough already. I have chosen to review three areas in more detail.

## A gel of historical and practical interest

I have explained the reasons why micelles form in a polar solvent like water. They can also form in a non polar solvent, but their structure is reversed. The hydrocarbon chains are on the outside of the micelle, partially penetrated by the solvent in which they are soluble. The polar head groups are in the centre of the micelle, remote from the solvent. One of the driving forces producing micelles is the bonding between the head groups, which can be of various types. In the case of aluminium soaps[7], the bonding is so strong that large rod-like micelles appear to be formed. Because of this asymmetry the viscosities of their solutions are high, and if the structures are broken up they reform spontaneously. The reversed micelle has a site where water can be solubilised, which is around the polar groups in the centre of the micelle. The presence of water affects the strength of the bonds between the head groups, and therefore can affect the viscosities of the resulting gels. The use of aluminium stearate is well known in pharmacy as a gelling agent for non aqueous systems, eg. procaine penicillin suspended in refined peanut oil using two per cent aluminium monostearate as a gelling agent.

There is a more widespread use of aluminium soaps than most people realise, as they are important constituents of the fire bomb and flame thrower material, Napalm. James McBain, who had first described a soap micelle in 1913, was Professor of Chemistry at Stanford University at the time of the second world war. Here he was joined by Karol Mysels, who as a young Pole, anticipated Hitler's intentions, and emigrated to the United States. Together they conducted a study on the structure and properties of Napalm[8].

Most of the initial development work on Napalm was done in 1941–42. The basic idea was to make a gel form of petrol or gasolene. Both British and American workers started by dissolving rubber in petrol. However, events at Pearl Harbour and after, prevented the free use of rubber and caused the experimenters to look at the metal soaps. These at first appeared unsatisfactory, as one of the criteria for the product was that it could be prepared in the cold, and filled into weapons on the battlefield. An 'aluminium palmitate' product was used, and by combination with aluminium naphthenate, the petrol was easily gelled, and the naphthenate/palmitate combination led to the name Napalm[8]. It turned out that the palmitate product was the aluminium soap of the total fatty acids of coconut oil, and that lauric acid, rather than the palmitic acid, played an important role in the gelling process. Nevertheless, the original name was retained. There are obviously complex micelles formed in the non aqueous medium, and their properties condition the performance of the product. They make the material tough and stringy in order not to be too widely dispersed by an explosive charge. The Napalm must also be easily ignited, but as the product is 92–94 per cent petrol this does not pose problems.

The product must be able to flow in pipes, and changes occur in the structure of the micelles when shearing forces are applied. One of the first pieces of evidence of viscous drag reduction arose from work carried out on Napalm just after the war[10]. Studies were made of the amount of petrol or Napalm flowing in the same pipe under different pressures (Fig. 6). At low pressures the viscous Napalm flowed more slowly than the petrol; but at high pressures, the Napalm flowed faster than the substances from which it was made. The modes of flow are different, and it is possible that the presence of the micelles keeps the flow of the Napalm streamlined at high pressures, while that of petrol becomes turbulent, and hence less effective.

This is a curious application of micellisation. Production of Napalm reached 75 million lb a year towards the end of the war. The effects were horrific. Stimpson[11] states that the first fire bomb raid on Japan did more damage and inflicted more casualties than the first atomic bomb.

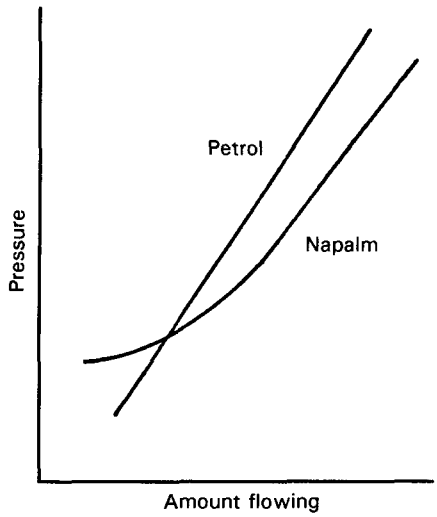


Fig. 6: Flow behaviour of petrol and napalm.

**Detergency**

I shall now examine how the properties of surface active agents and micelles are applied in the very complex problem of the cleaning of fabrics and surfaces[11], which is an important problem in pharmacy and many other areas. The aim is to remove unwanted soil from a dirty surface. The evaluation of this process may be open to criticism because the principal evaluators for fabrics are people who operate washing machines, and they use the visual appearance of fabric as a criterion, and not the amount of soil remaining on it. Therefore if you brighten the surface by means of optical whitener, and brainwash the observers with the visual surfactant of television, you are likely to convince people that they are making things cleaner. Clutch your box of 'Sudso' to your bosom, mother, it is one of the few things you have to hold on to in this chaotic world. We therefore accept things which are clean for a purpose; eg, a dispensary bench free of soil, but having present a few traces of surfactant from the washing liquor. A cloth also free of soil, but contaminated with an optical whitener and a softening finisher.

The principal stages of the process are to apply the cleaning liquid to the soiled substrate, to apply suitable agitation to separate substrate and soil, and then to separate the substrate from the liquid and rinse it.

Substrates fall into two main classes; hard surfaces having a small surface/mass ratio, and textiles which have a large surface/mass ratio, and which also have very complicated surface properties. Soils may be solid or liquid in nature, and there are different mechanisms for the ways in which they are removed from the surfaces.

As I am concerned here with the general physicochemical phenomena that occur in detergency, I will use the surface active properties which were discussed earlier in an explanation of detergency rather than review the 15 to 20 components that may be present in commercial washing formulation.

The removal of the solid particle of soil from the substrate is really the production of soil or suspension of the soil. The work of adhesion, W, between the substrate and soil is:

$$W_{subs/D} = D_w + _{subs/w} - _{subs/D}$$

where subs = substrate, D = dirt, w = water. The detergent lowers the interfacial energies ( ) between dirt/water and substrate/water, so decreasing the work of adhesion between substrate and dirt. Mechanical agitation can then detach it from the surface. The detergent is adsorbed at the relevant interfaces, so with an anionic surfactant electrical repulsions develop between the polar head groups of surfactants adsorbed on the substrate and the soil.

The soil particle itself may consist of an agglomerate of many fine particles, in which case a sol is formed on removal from the substrate. We are therefore back to the classical colloid stability problem; having displaced the solid from the surface, we want to prevent it coagulating again on to the substrate. There is the balance between van der Waals' attractive forces between the particles and substrate, and the repulsive forces due to the electrical double layer or to entropic factors. At close distances of approach between particles and substrate, the repulsive forces must predominate to prevent redeposition of soil. The surfactant is responsible for preventing this coagulation. To quote Ostwald[13], speaking in 1938: 'If a professor is obliged to discuss the unsatisfactory condition of the theory of coagulation for 30 or more years, in every term of the academic year, then it may easily happen that he becomes more and more impatient. Either he becomes resigned or he commences to curse. The latter course is in general more fruitful.'

For removal of liquid soils, the contact angle is one of prime importance. The contact angle of 180° means that the surface is covered by a thin film of oil (Fig. 7).

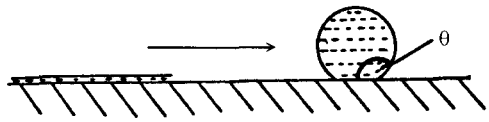


Fig. 7: Rolling up of oil at a surface. $\theta$ = contact angle.

The detergent can alter the contact angle so that the oil 'rolls up' and is easily detached from the surface agitation. In simple terms adsorption of surfactant on the substrate is pushing the oil into globules. The contact angle may not necessarily become zero for removal of oil. At contact angles of 90°, large oil droplets can be removed by hydraulic currents arising from agitation. Emulsification provides a mechanism by which oil can be removed from the surface. The oil/water emulsion must be formed under the conditions of agitation prevailing in the cleaning process, so in general it must form under conditions of mild agitation. The emulsification mechanism may not work if there is a poor fit in the hydrophilic–lipophilic balance values of the soil and the detergent and sometimes fatty acids are added to the bath to combine with the soil and make it more readily emulsifiable. The prime role of the surfactant is to lower the interfacial tension between oil and water, and thus to aid the formation of a relatively stable emulsion.

In most of what I have said about detergency, it has been the surface properties of the detergent which have been important, rather than their micellar properties. However, solubilisation provides another mechanism for soil removal, the non polar oil being taken into the micelle. The more non polar the oil, the deeper it penetrates into the micellar structure. Solubilising capacity is in general fairly low for non polar materials; if semi polar groups are present in the soil molecules, there can be a considerable increase in solubilising capacity. Solubilisation can be a useful mechanism for taking up any small amounts of oil left on the substrates after the 'roll back' phenomena have occurred.

If high detergent concentrations are used, one may reach parts of the oil–water–surfactant phase diagram, where single phases exist, which are often liquid crystalline in nature. Formation of a liquid crystal with the soil, and displacement of it from the surface by agitation provides another mechanism for soil removal. This is an example of solubilisation in concentrated surfactant solutions.

In the removal of both solids and liquids, adsorption of surfactant at substrate/water and dirt/water interfaces cuts down the work of adhesion, and helps the release of soil. Adsorption of surfactant at the air/water interface of the detergent bath, with the subsequent development of foam does not mean a detergent is being effective. However, it does provide a pretty gimmick for advertising purposes, and many people are brainwashed by foam, even when they only get it on their hands. While it would be nice to have a 'No Sudso' product for use by those experienced in colloid and surface science, the market for such a product is lamentably small.

**Liposomes**

Liposomes are structures which have extremely exciting possibilities in the field of drug research. Their principal component is lecithin, which is a glycerophosphatidyl–choline molecule esterified by two long chain fatty acids (Fig. 1). It forms part of the cell wall structure in animals and man. For many years it has been known that when a drop of water is placed on a piece of solid lecithin structures grow out from it; these are called myelin forms. They consist of a lecithin/water mixture and are probably liquid crystals; their growth reflects the ease with which lecithin forms itself into bimolecular leaflets. The hydrocarbon chains are directed inwards in the structure, getting away from the water for the reasons given earlier. The polar head of the molecule consists of a positively charged quaternary nitrogen, and a negative charge from ionisation of the tertiary phosphate

hydrogen. The head groups, by a suitable arrangement, can attract one another in the plane of the sheet of groups. The bimolecular leaflet (Fig. 8) is essentially a very large micelle. One can easily see why it is a cell wall component. It is a bimolecular leaflet whose surfaces can adsorb protein, and whose interior can take up cholesterol-like compounds, to give the type of structure envisaged for the cell wall by Danielli.

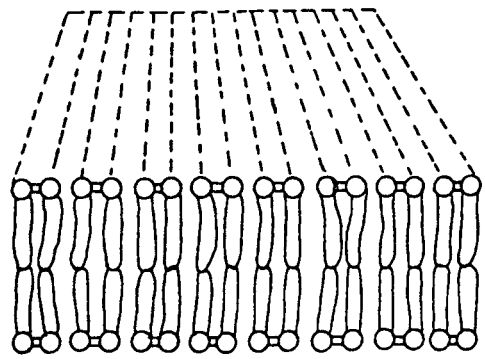

Fig. 8: Bimolecular leaflet of lecithin: ○ = polar groups. ⬭ = hydrocarbon chains.

In 1953 Professor Leonard Saunders[14] published a paper describing how he had made an interface between two miscible liquids, a lecithin sol and water, and how he had demonstrated that it had mechanical strength. The structure had obvious promise as a model of a cell wall. I spent the next three years working under Professor Saunders, pulling pieces of platinum wire through this structure in order to learn more about its mechanical strength.

The lecithin sols we used then were turbid because the particle size was large. Later it was shown that ultrasonic irradiation reduced the particle size, until the sol was optically clear, giving micellar weights in the region $4–50 \times 10^6$ . It was also shown that when cholesterol and lecithin were dissolved in a common solvent, which was evaporated off after mixing it with water, and the system then subjected to ultrasound, a clear dispersion was obtained containing up to 10 per cent cholesterol[15]. I am fairly sure that the structures formed in the solution were what we call liposomes today. A typical liposome preparation[16] consists of dissolving lecithin, cholesterol, and dicetyl phosphate in chloroform, evaporating off the solvent to give a thin solid film, and shaking this with phosphate buffer. The suspension is ultrasonically irradiated.

Investigation by electron microscopy[17] shows that the liposome consists of a central pool of water surrounded by the bimolecular leaflet. For the single bilayer shell the external radius is about 120Å. Other layers may be present giving aqueous compartments surrounded by bimolecular leaflets. The longer the period of irradiation the smaller the liposome becomes. Drugs and enzymes can be entrapped in the aqueous compartments, and it is claimed that the small size of the liposomes makes it possible for them to cross biological membranes easily. During preparation the drug is placed in the aqueous phase.

Liposomes are examples of lecithin micelles which have turned back on themselves, and the ends of the bimolecular sheets have joined up to give a sphere. They can be separated from non liposomal material by gel chromatography or ultrafiltration.

Clearly the permeability of the liposomal wall is an important factor in controlling drug release from this type of structure. Increasing the unsaturation of the lipids increases the permeability to water, and the incorporation of cholesterol decreases the permeability[18]. Permeability effects are believed to be related to the fluidity of the lipid structures. The charge on the surface of the liposomes affects the permeability to charged species[19,20]. Negatively charged liposomes are permeable to anions, but positively charged ones are impermeable to cations. The permeability of negatively charged liposomes depends on the magnitude of the charge on the surface.

When a drug is entrapped in liposomes, that rate of clearance of the liposomes is important in controlling biological activity. Juliano and Stamp[21] injected preparations intravenously into rats and showed that $^{3}H$ labelled colchicine was cleared more slowly than free colchicine which was not trapped in liposomes.

A number of factors affecting clearance have been elucidated. Unilamellar liposomes are cleared more slowly than multilamellar types where the liposomes have a neutral charge. For a liposome preparation to stay in the body as long as possible the drug should be entrapped in the unilamellar type. Positively charged liposomes show very similar behaviour to that of the neutral type, but negatively charged ones are cleared very rapidly, and the clearance rate is independent of size. It may be that the negatively charged structures aggregate due to contact with calcium ions which will increase their effective size and their rate of clearance, or there may be a specific mechanism for anion transport. It appears that the complex kinetic pattern given by the normal liposome preparation is due to the heterogeneity of the particles involved. Homogeneous preparations, obtained by fractionation, give a simpler kinetic picture.

## Applications and potential application of liposomes in drug treatment

Gregoriadis[22] had studied two drugs administered to rats. Actinomycin D was chosen because it is harmful to rapidly dividing non malignant cells, and the liposome might provide a way of targeting the drug to the malignant cells. The drug in positively charged liposomes was retained in the plasma for a considerable time, while free actinomycin was rapidly cleared (Fig. 9). If the radioactivity is measured in different organs (Fig. 10) from animals killed at various times after the intravenous injection, it is clear that initially the free drug gives fairly high concentrations in the liver, but as time goes on concentration falls. The liposomes are held fairly strongly by the liver and would therefore be able to release slowly actinomycin to this organ. Results for the small intestine show a considerable amount of radioactivity from the free drug whereas the liposome preparation gives very little activity at this site. Therefore the liposomes, by keeping the drug at the required site, and by keeping it from the rapidly dividing cells of the intestine, may prevent damage to healthy cells.

Benzylpenicillin was chosen for study because of its failure to penetrate the cells of the reticuloendothelial system, eg, spleen, when used in antimicrobial therapy. The blood level picture for benzylpenicillin is like that for actinomycin, in that the liposomal preparations caused the drug to be cleared much more slowly than free drug. The results for individual organs again show how much more effective the liposomal preparations are at getting drug into the liver than when the free drug only is used. Although the concentrations in the spleen are small, liposomes give three to four times more drug in the spleen than is achieved by injection of free drug, so the object of the exercise – getting the drug to a place it does not normally go – has been achieved.

Liposomes have been used as carriers for the oral administration of insulin and that would represent considerable progress over the use of repeated injections[23].

It has been suggested[15] that liposomes could be used in enzyme replacement therapy, where a specific enzyme is lacking in one or more tissues. The conventional treatment for this type of condition involves the direct administration of the necessary enzymes to remove the accumulating substrates. If the preparation is derived from animal sources then there is the risk of immunological reaction, and also the undesirability of having certain enzymes in the general circulation. Entrapment in liposomes could help to overcome these problems. Amyloglucosidase has been entrapped and has potential uses in the treatment of glycogen storage diseases. The liposomes are disrupted in the liver, freeing the enzyme to exert its action on stored glycogen. Invertase and cyclic adenosine monophosphate have also been prepared in liposomes.

Gregoriadis and Allison[24] have suggested the use of liposomes as immunological adjuvants. Diphtheria toxoid has been given to mice subcutaneously. The antigens give rise to the production of more antibodies than

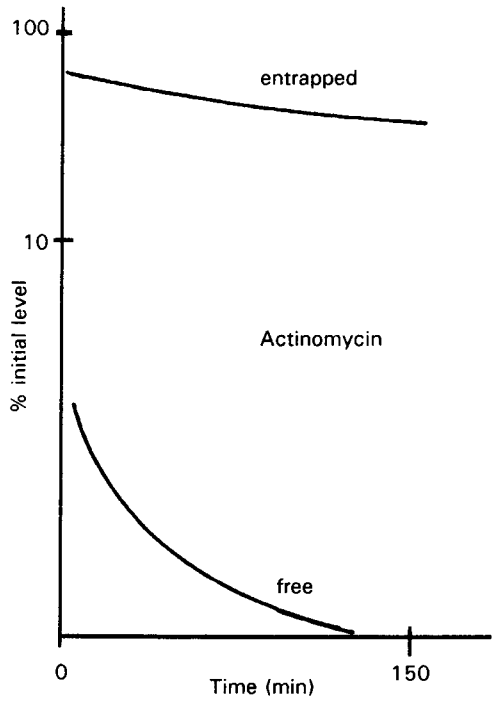


Fig. 9: Plasma levels of actinomycin after injection of free drug or drug entrapped in liposomes[22].

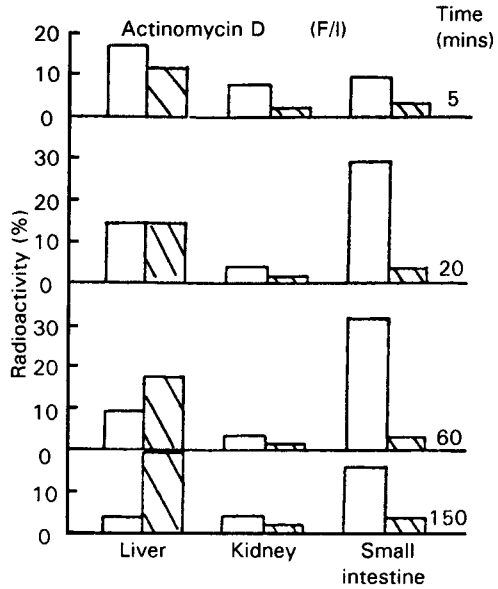


Fig. 10: Tissue levels of actinomycin. Shaded rectangles represent drug in the liposome preparation, and open rectangles represent free drug[22].

the same dose of free antigen. Entrapment prevents serum sickness developing when diphtheria toxoid is given intravenously.

I have mentioned that liposomes often gather in the liver and spleen, and one of the most exciting prospects is that of targeting them to various organs. It might be possible to manipulate the surface of the lipid particles. Molecular probes, which show affinity for the surfaces of certain normal or malignant cells, have been incorporated. The use of immunoglobulin G as a probe[25] led to the uptake of liposomes by those cells against which the immunoglobulin had been raised. It is possible that in attachment to the cell surface, the

immunoglobulin caused uptake of the entire liposome and it is likely that the immunologically active part of the molecule was exterior to the liposome.

The development of liposomes as drug carriers for enzyme replacement and for targeting is at a very early stage. There is however great promise in this field, as you can see from the examples I have outlined. A number of more remote possibilities have been raised, one of which is to administer messenger RNA and DNA in genetic disorders, so putting missing segments into defective cells. I will not dwell on what else might be done with this approach. Another possibility is to prepare alcohol dehydrogenase in liposomes targeted to the liver. The alcoholic will then get very little central nervous system action from drinking; he will get a nasty flood of acetaldehyde to give him a hangover from the euphoria he did not experience, and once the liposomes are in place he cannot prevent them from working.

It is a long road from 1913 to 1976, and there have been many developments along the way; some good, some bad, some shocking. Efficient cleaning, foam filled rivers, defoliation by Napalm. Clearly the micelles have not got cleverer, but the technology and knowledge of those who use them have grown.

I have called it a long road, and Walt Whitman wrote in his poem 'The Road' a passage which to me epitomises scientific progress; 'Now understand me well – it is provided in the essence of things that from any fruition of success, no matter, what shall come forth something to make a greater struggle necessary'.

*Acknowledgements*

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