Pharmaceutics

The science of dosage form design

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DISPERSE SYSTEMS

A disperse system may be defined as a system in which one substance, the disperse phase, is dispersed as particles throughout another, the dispersion medium.

Although systems in which the size of the dispersed particles are within the range of about 10^{-9} m (1 nm) to 10^{-6} m (1 μm) are termed colloidal, and have specific properties, there is no sharp distinction between colloidal and non-colloidal systems, particularly at the upper size limit. For example the droplet size in emulsions, the particle size in suspensions and the natural systems of micro-organisms and blood are normally in excess of 1 μm and yet such dispersions show many of the properties of colloidal systems. Some examples of the different disperse systems are given in Table 6.1.

The essential character common to all disperse systems is the large area to volume ratio for the particles involved, for example, when a cube of 1 cm edge is subdivided into cubes of 100 nm edge there is a 10^5 increase in surface area and associated free energy. This free energy will be decreased if the particles aggregate or coalesce because of the reduction in interfacial area that accompanies such aggregation. Since any system will tend to react spontaneously to decrease its free energy to a minimum it follows that disperse systems are often unstable, the particles aggregating rather than remaining in contact with the dispersion medium. Dispersions that exhibit this behaviour are termed *lyophobic*, or solvent hating, dispersions. In other systems known as *lyophilic*, solvent loving, dispersions an affinity exists between the dispersed particles and the dispersion medium and this contributes to the stability of these systems. The terms *hydrophobic* and *hydrophilic* may be used when the dispersion medium is water.

Whilst the majority of dispersions used in pharmacy are aqueous they are by no means limited to water, thus dispersions of solids in oils include

Table 6.1 Types of disperse systems

Dispersed phase	*Dispersion medium*	*Name*	*Examples*
Liquid	Gas	Liquid aerosol	Fogs, mists, aerosols
Solid	Gas	Solid aerosol	Smoke, powder aerosols
Gas	Liquid	Foam	Foam on surfactant solutions
Liquid	Liquid	Emulsion	Milk, pharmaceutical emulsions
Solid	Liquid	Sol, suspension	Silver iodide sol, aluminium hydroxide suspension
Gas	Solid	Solid foam	Expanded polystyrene
Liquid	Solid	Solid emulsion	Liquids dispersed in soft paraffin, opals, pearls
Solid	Solid	Solid suspension	Pigmented plastics, colloidal gold in glass (ruby glass)

suspensions for injection and oral use and suspensions of solids in aerosol propellants.

This chapter is an attempt to describe colloidal systems and to show how their properties may be applied to the study of coarse dispersions of pharmaceutical interest.

COLLOID SCIENCE

Colloid science concerns systems in which one or more of the components has at least one dimension within the range of about 1 nm to 1 μm and thus includes shapes such as spheres, cubes, ellipsoids, rods, discs and random coils, where other dimensions may be significantly larger than 1 μm. As indicated, some colloids can be broadly classified as those that are lyophobic, these dispersions or *sols* are thermodynamically unstable and the particles tend to aggregate to lower the surface free energy of the system. They are irreversible systems in the sense that they are not easily reconstituted after phase separation. Water-insoluble drugs and clays such as kaolin and bentonite and oils form lyophobic dispersions. On the other hand macromolecular material such as the proteins, tragacanth and methylcellulose form lyophilic sols which, as true solutions, are thermodynamically stable. These are reversible systems because, after separation of solute from solvent, they are easily reconstituted. Surfactant molecules, because of their affinity for water and their tendency to form micelles which are of colloidal dimensions, form hydrophilic colloidal dispersions in water but are usually classified separately as *association colloids*, the older term being colloidal electrolyte.

It has been suggested that the efficiency of certain substances, used in pharmaceutical preparations, may be increased if colloidal forms are used since these have large surface areas. Thus, for example, the adsorption of toxins from the gastrointestinal tract by kaolin, and the rate of neutralization of excess acid in the stomach by aluminium hydroxide, may be increased if these compounds are used in colloidal form.

In the purification of proteins, use is made of the changes in solubility of colloidal material with alteration of pH and addition of electrolyte.

The protective ability, or, as it is now known, the *steric stabilization* effect of hydrophilic colloids is used to prevent the coagulation of hydrophobic particles in the presence of electrolytes. Thus hydrophobic sols for injection, such as colloidal gold (^{198}Au) injection, must be sterically stabilized in this case by gelatin. Hydrophilic sols are viscous and use is made of this property in retarding the sedimentation of particles in pharmaceutical suspensions.

Blood plasma substitutes such as dextran, polyvinylpyrrolidone and gelatin are hydrophilic colloids which exert an osmotic pressure similar to that of plasma and are thus used to restore or maintain blood volume.

Iron–dextran complexes form non-ionic hydrophilic sols suitable for injection for the treatment of anaemia.

Preparation of colloids

Lyophilic colloids

The affinity of lyophilic colloids for the dispersion medium leads to the spontaneous formation of colloidal dispersions. For example, acacia, tragacanth, methylcellulose and certain other cellulose derivatives disperse in water. This simple method of dispersion is a general one for the formation of lyophilic colloids.

Lyophobic colloids

The preparative methods for lyophobic colloids may be divided into those methods that involve the breakdown of larger particles into particles of colloidal dimensions (dispersion methods) and those in which the colloidal particles are formed by aggregation of smaller particles such as molecules (condensation methods).

Dispersion methods

The breakdown of coarse material may be effected by the use of a colloid mill or ultrasonics.

Colloid mills These mills cause the dispersion of coarse material by shearing in a narrow gap between a static cone (the stator) and a rapidly rotating cone (the rotor).

Ultrasonic treatment The passage of ultrasonic waves through a dispersion medium produces alternating regions of cavitation and compression in the medium. The cavities collapse with great force and cause the breakdown of coarse particles dispersed in the liquid.

With both these methods the particles will tend to reunite unless a stabilizing agent such as a surface-active agent is added.

Condensation methods

These involve the rapid production of supersaturated solutions of the colloidal material under conditions in which it is deposited in the dispersion medium as colloidal particles and not as a precipitate. The supersaturation is often obtained by means of a chemical reaction that results in the formation of the colloidal material. For example, colloidal silver iodide may be obtained by reacting together dilute solutions of silver nitrate and potassium iodide, sulphur from sodium thiosulphate and hydrochloric acid solutions, and ferric chloride boiled with excess of water produces colloidal hydrated ferric oxide.

A change in solvent may also cause the production of colloidal particles by condensation methods. If a saturated solution of sulphur in acetone is poured slowly into hot water, the acetone vaporizes leaving a colloidal dispersion of sulphur. A similar dispersion may be obtained when a solution of a resin, such as benzoin in alcohol, is poured into water.

Dialysis

Colloidal particles are not retained by conventional filter papers but are too large to diffuse through the pores of membranes such as those made from regenerated cellulose products, e.g. collodion (cellulose nitrate evaporated from a solution in alcohol and ether) and cellophane. The smaller particles in solution are able to pass through these membranes. Use is made of this difference in diffusibility to separate micromolecular impurities from colloidal dispersions. The process is known as dialysis. The process of dialysis may be hastened by stirring so as to maintain a high concentration gradient of diffusible molecules across the membrane and by renewing the outer liquid from time to time.

Ultrafiltration By applying pressure (or suction) the solvent and small particles may be forced across a membrane whilst the larger colloidal particles are retained. The process is referred to as ultrafiltration. It is possible to prepare membrane filters with known pore size and use of these allows the particle size of a colloid to be determined. However, particle size and pore size cannot be properly correlated because the membrane permeability is affected by factors such as electrical repulsion, when both the membrane and particle carry the same charge, and particle adsorption which can lead to blocking of the pores.

Electrodialysis An electric potential may be used to increase the rate of movement of ionic impurities through a dialysing membrane and so provide a more rapid means of purification. The concentration of charged colloidal particles at one side and at the base of the membrane is termed electrodecantation.

Pharmaceutical applications of dialysis These include the use of membrane filters, artificial membranes as models for the diffusion of drugs through natural membranes, in the study of drug/protein binding and as the principle of haemodialysis where small molecular weight impurities from the body are removed by passage through a membrane.

Properties of colloids

Kinetic properties

In this section several properties of colloidal systems, which relate to the motion of particles with respect to the dispersion medium, will be considered. Thermal motion manifests itself in the form of Brownian motion, diffusion and osmosis. Gravity (or a centrifugal field) leads to sedimentation. Viscous flow is the result of an externally applied force. Measurement of these properties enables molecular weights or particle size to be determined.

Brownian motion

Colloidal particles are subject to random collisions with the molecules of the dispersion medium with the result that each particle pursues an irregular and complicated zig-zag path. If the particles (up to about 2 μm diameter) are observed under a microscope or the light scattered by colloidal particles is viewed using an ultramicroscope, the erratic motion seen is referred to as Brownian motion after Robert Brown (1827) who first observed this phenomenon with pollen grains suspended in water.

Diffusion

As a result of Brownian motion colloidal particles spontaneously diffuse from a region of higher concentration to one of lower concentration. The rate of diffusion is expressed by Fick's first law

$$\frac{dm}{dt} = -DA \frac{dC}{dx} \tag{6.1}$$

where dm is the mass of substance diffusing in time dt across an area A under the influence of a concentration gradient dC/dx. (The minus sign denotes that diffusion takes place in the direction of decreasing concentration.) D is the diffusion coefficient and has the dimensions of area per unit time. The diffusion coefficient of a dispersed material is related to the frictional coefficient of the particles by Einstein's law of diffusion

$$Df = kT \tag{6.2}$$

where k is the Boltzmann constant and T temperature.

Therefore as the frictional coefficient f is given by Stokes

$$f = 6\pi\eta a \tag{6.3}$$

where η is the viscosity of the medium and a the radius of the particle, as a sphere

$$D = \frac{kT}{6\pi\eta a} = \frac{RT}{6\pi\eta aN} \tag{6.4}$$

where N is the Avogadro number and R is the universal gas constant. The diffusion coefficient may be obtained by an experiment measuring the change in concentration, via refractive index gradients, of the free boundary which is formed when the solvent and solution are brought together and allowed to diffuse. The diffusion coefficient can be used to obtain the molecular weight of an approximately spherical particle, such as egg albumin and haemoglobin, by using Eqn 6.4 in the form

$$D = \frac{RT}{6\pi\eta N} \cdot \sqrt[3]{\frac{4\pi N}{3M\bar{v}}} \tag{6.5}$$

where M is the molecular weight and $\bar{v}$ the partial specific volume of the colloidal material.

Sedimentation

Consider a spherical particle of radius a and density σ falling in a liquid of density ρ and viscosity η. The velocity v of sedimentation is given by Stokes' law

$$v = \frac{2a^2 g(\sigma - \rho)}{9\eta} \tag{6.6}$$

where g is acceleration due to gravity.

If the particles are only subjected to the force of gravity then, due to Brownian motion, the lower size limit of particles obeying Eqn 6.6 is about 0.5 μm. A stronger force than gravity is therefore needed for colloidal particles to sediment and use is made of a high speed centrifuge, usually termed an ultracentrifuge, which can produce a force of about $10^6 g$. In a centrifuge, g is replaced by $\omega^2 x$, where ω is the angular velocity and x the distance of the particle from the centre of rotation and Eqn 6.6 becomes

$$v = \frac{2a^2 (\sigma - \rho) \omega^2 x}{9\eta} \tag{6.7}$$

Modification of the sedimentation method using the ultracentrifuge is used in two distinct ways in investigating colloidal material.

In the sedimentation velocity method a high centrifugal field is applied — up to about $4 \times 10^5 g$ — and the movement of the particles, monitored by changes in concentration, is measured from time to time.

In the sedimentation equilibrium method, the colloidal material is subjected to a much lower

centrifugal field until sedimentation and diffusion tendencies balance one another, and an equilibrium distribution of particles throughout the sample is attained.

Sedimentation velocity The velocity dx/dt of a particle in a unit centrifugal force can be expressed in terms of the Svedberg coefficient s,

$$s = \frac{dx/dt}{\omega^2 x} \tag{6.8}$$

Under the influence of the centrifugal force particles pass from position x_1 at time t_1 to position x_2 at time t_2 — the differences in concentration with time can be measured using changes in refractive index and the application of the schlieren optical arrangement whereby photographs can be taken showing these concentrations as peaks. Integration of Eqn 6.8 using the above limits gives

$$s = \frac{\ln x_2/x_1}{\omega^2 (t_2 - t_1)} \tag{6.9}$$

By suitable manipulation of Eqns 6.7, 6.8 and 6.9 an expression giving molecular weight M can be obtained

$$M = \frac{RTs}{D(1 - \bar{\nu}\rho)} = \frac{RT \ln x_2/x_1}{D(1 - \bar{\nu}\rho)(t_2 - t_1)\omega^2} \tag{6.10}$$

where $\bar{\nu}$ is the specific volume of the particle.

Sedimentation equilibrium Equilibrium is established when sedimentation and diffusional forces balance. Combination of sedimentation and diffusion equations is made in the analysis and

$$M = \frac{2RT \ln C_2/C_1}{\omega^2 (1 - \bar{\nu}\rho)(x_2^2 - x_1^2)} \tag{6.11}$$

where C_1 and C_2 are the sedimentation equilibrium concentrations at distances x_1 and x_2 from the axis of rotation.

Unfortunately in order to obtain equilibrium the centrifuge has to be run for about a week, with consequent experimental difficulties. A technique has therefore been developed which allows analysis to be made at intervals during the early stages of the experiment. Mathematical treatment of the results can then be used to obtain the molecular weight.

Osmotic pressure

The determination of molecular weights of dissolved substances from colligative properties is standard procedure but of these, osmotic pressure is the only one with a practical value in the study of colloidal particles. For example, consider a solution of 1 g of macromolecular material of molecular weight 70 000 dissolved in 100 cm^3 of water. Assuming ideal behaviour, the depression of the freezing point is 0.0026 K and the osmotic pressure at 20 °C, 350 N m^{-2} or about 35 mm of water. The above freezing point depression is far too small to be measured with sufficient accuracy by conventional methods and, of rather greater importance, the presence of about 1 mg of impurity of molecular weight 50 would more than double the above value. Not only does the osmotic pressure provide an effect which is measurable, but also the effect of any low molecular weight material, which can pass through the membrane is virtually eliminated.

However, the usefulness of osmotic pressure measurement is limited to a molecular weight range of about 10^4 to 10^6; below 10^4 the membrane may be permeable to the molecules under consideration and above 10^6 the osmotic pressure will be too small to permit accurate measurement.

If a solution and solvent are separated by a semipermeable membrane the tendency to equalize chemical potentials (and hence concentrations) on either side of the membrane results in a net diffusion of solvent across the membrane. The pressure necessary to balance this osmotic flow is termed the osmotic pressure.

For a colloidal solution the osmotic pressure π can be described by

$$\pi/C = RT/M + BC \tag{6.12}$$

where C is the concentration of the solution, M the molecular weight of the solute and B a constant depending on the degree of interaction between the solvent and solute molecules.

Thus a plot of π/C verses C is linear with the value of the intercept as $C \rightarrow 0$ giving RT/M enabling the molecular weight of the colloid to be calculated.

The Donnan membrane effect

The diffusion of small ions through a membrane will be affected by the presence of a charged macromolecule that is unable to penetrate the membrane because of its size. At equilibrium the distribution of the diffusible ions is unequal, being greater on the side of the membrane containing the non-diffusible ions. This is known as the Donnan membrane effect. For a full discussion, the reader is referred to Shaw (1980).

Application of this principle suggests that co-administration of a large concentration of an anionic macromolecule, e.g. sodium carboxymethylcellulose, with a diffusible anion, e.g. potassium benzylpenicillin, should enhance the diffusion of the benzylpenicillin anion across body membranes.

Viscosity

Viscosity is an expression of the resistance to flow of a system under an applied stress and these properties are discussed in detail in Chapter 2. Some of those relationships are repeated here.

Einstein developed an equation of flow applicable to colloidal dispersions of spherical particles,

$$\eta = \eta_o (1 + 2.5\ \phi) \qquad (6.13)$$

where η_o is the viscosity of the dispersion medium and η the viscosity of the dispersion when the volume fraction of colloidal particles present is ϕ.

A number of viscosity coefficients may be defined with respect to Eqn 6.13. These include *relative viscosity*

$$\eta_{rel} = \eta/\eta_o = 1 + 2.5\ \phi \qquad (6.14)$$

specify viscosity

$$\eta_{sp} = \eta/\eta_o - 1 = (\eta - \eta_o)/\eta_o = 2.5\ \phi$$

or

$$\eta_{sp}/\phi = 2.5 \qquad (6.15)$$

Since volume fraction is directly related to concentration Eqn 6.15 may be written as

$$\eta_{sp}/C = K \qquad (6.16)$$

where C is the concentration expressed as grams of colloidal particles per 100 ml of total dispersion. If η is determined for a number of concentrations of macromolecular material in solution, η_{sp}/C plotted versus C and the line obtained extrapolated to infinite dilution the constant obtained is $[\eta]$ known as the *intrinsic viscosity*.

This constant may be used to calculate the molecular weight of the macromolecular material by making use of the Mark–Houwink equation

$$[\eta] = KM^{\alpha} \qquad (6.17)$$

where K and α are constants characteristic of the particular polymer–solvent system. These constants are obtained initially by determining $[\eta]$ for a polymer fraction whose molecular weight has been determined by another method such as sedimentation, osmotic pressure or light scattering. The molecular weight of the unknown polymer fraction may then be calculated. This method is suitable for use with polymers like the dextrans used as blood plasma substitutes.

Optical properties

Light scattering

When a beam of light is directed at a colloidal sol some of the light may be absorbed (when light of certain wavelengths is selectively absorbed a colour is produced), some is scattered and the remainder transmitted undisturbed through the sample. Due to the light scattered the sol appears turbid; this is known as the Tyndall effect. The turbidity of a sol is given by the expression

$$I = I_o \exp^{-\tau l} \qquad (6.18)$$

where I_o is the intensity of the incident beam, I that of the transmitted light beam, l the length of the sample and τ the turbidity.

Light scattering measurements are of great value for estimating particle size, shape and inter-

actions, particularly of dissolved macromolecular materials, as the turbidity depends on the size (molecular weight) of the colloidal material involved. Measurements are simple in principle but experimentally difficult because of the need to keep the sample free from dust, the particles of which would scatter light strongly and introduce large errors.

As most colloids show very low turbidities, instead of measuring the transmitted light (which may differ only marginally from the incident beam), it is more convenient and accurate to measure the scattered light, at an angle — usually 90° — relative to the incident beam.

The turbidity can then be calculated from the intensity of the scattered light, provided the dimensions of the particle are small compared to the wavelength of the light used, by the expression

$$\tau = \frac{16\pi}{3} R_{90°} \qquad (6.19)$$

$R_{90°}$ is given by $I_\theta r^2/I_\theta$ known as the Rayleigh ratio — where I_θ is the intensity of the scattered and I_θ the incident, light; r is the distance from the scattering particle to the point of observation. By use of the so-called fluctuation theory of statistical mechanics whereby light scattering is treated as a consequence of random non-uniformities of concentration, and hence refractive index, arising from random molecular movement the following relationship between turbidity and molecular weight was derived by Debye in 1947:

$$HC/\tau = 1/M + 2BC \qquad (6.20)$$

C is the concentration of the solute and B an interaction constant allowing for non-ideality. H is an optical constant for a particular system depending on refractive index changes with concentration and the wavelength of light used. A plot of HC/τ against concentration results in a straight line of slope $2B$. The intercept on the HC/τ axis is $1/M$ allowing the molecular weight to be calculated.

Light scattering measurements are particularly suitable for finding the size of association colloids and the number of molecules of surface-active agent forming them and for the study of proteins and natural and synthetic polymers.

It can be shown that the intensity of the scattered light is inversely proportional to the wavelength λ of the light used; so that blue light ($\lambda \approx 450$ nm) is scattered much more than red light ($\lambda \approx 650$ nm). With incident white light, a scattering material will, therefore, tend to be blue when viewed at right angles to the incident beam and red when viewed from end on — evident in the blue colour of the sky, tobacco smoke etc., and the yellowish-red of the rising and setting sun.

Ultramicroscope

Colloidal particles are too small to be seen with an optical microscope. Light scattering is made use of in the ultramicroscope first developed by Zsigmondy, in which a cell containing the colloid is viewed against a dark background at right angles to an intense beam of incident light. The particles, which exhibit Brownian motion, appear as spots of light against the dark background. The ultramicroscope is used in the technique of microelectrophoresis for measuring particle charge.

Electron microscope

The electron microscope, capable of giving actual pictures of the particles, is used to observe the size, shape and structure of colloidal particles. The success of the electron microscope is due to its high resolving power, defined in terms of d, the smallest distance by which two objects are separated yet remain distinguishable. The smaller the wavelength of the radiation used the smaller is d and the greater the resolving power. An optical microscope, using visible light as its radiation source, gives a d of about 0.2 μm. The radiation source of the electron microscope is a beam of high energy electrons having wavelengths in the region of 0.01 nm, d is thus about 0.5 nm. The electron beams are focused using electromagnets and the whole system is under a high vacuum of about 10^{-5} to 10^{-6} mmHg to give the electrons a free path. With wavelengths of the order indicated the image cannot be viewed direct, so use is made of a fluorescent screen.

One big disadvantage of the electron microscope for viewing colloidal particles is that only dried

samples can be examined. Consequently it gives no information on solvation or configuration in solution and the particles may be affected by sample preparation.

Electrical properties

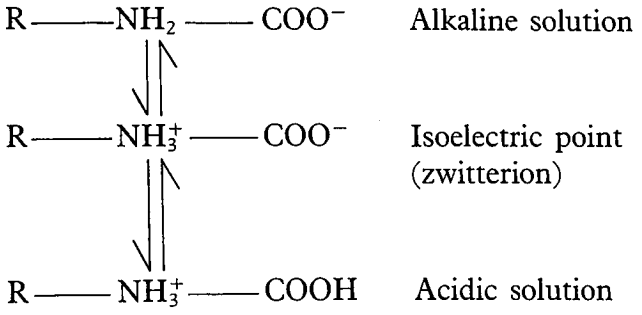
Electrical properties of interfaces

Most surfaces acquire a surface electric charge when brought into contact with an aqueous medium, the principal charging mechanisms being as follows.

Ion dissolution Ionic substances can acquire a surface charge by virtue of unequal dissolution of the oppositely charged ions of which they are composed, for example, silver iodide in a solution with excess [I^-] the particles will carry a negative charge, but the charge will be positive if excess [Ag^+] is present. Since the concentrations of Ag^+ and I^- determine the electric potential at the particle surface, they are termed potential determining ions. In a similar way H^+ and OH^- are potential determining ions for metal oxides and hydroxides such as magnesium and aluminium hydroxides.

Ionization Here the charge is controlled by the ionization of surface groupings, examples include the model system of polystyrene latex which frequently has carboxylic acid groupings at the surface which ionize to give negatively charged particles. In a similar way acidic drugs such as ibuprofen and nalidixic acid also acquire a negative charge.

Amino acids and proteins acquire their charge mainly through the ionization of carboxyl and amino groups to give $-COO^-$ and NH_3^+ ions. The ionization of these groups and so the net molecular charge depends on the pH of the system. At low pH the protein will be positively charged $-NH_2 \rightarrow NH_3^+$ and at high pH, negatively charged, $-COOH \rightarrow COO^-$. At a certain definite pH, specific for each individual protein, the total number of positive charges will equal the total number of negative charges and the net charge will be zero. This pH is termed the isoelectric point of the protein. The protein is probably ionized at the isoelectric point, existing in the zwitterion form but the apparent charge is zero. This may be represented as follows:



A protein is least soluble (the colloidal sol is least stable) at its isoelectric point and is readily desolvated by very water-soluble salts such as ammonium sulphate. Thus insulin may be precipitated from aqueous alcohol at pH 5.2.

Erythrocytes and bacteria usually acquire their charge by ionization of surface chemical groups such as sialic acid.

Ion adsorption A net surface charge can be acquired by the unequal adsorption of oppositely charged ions. Surfaces in water are more often negatively charged than positively charged, because cations are generally more hydrated than anions and so the former have the greater tendency to reside in the bulk aqueous medium whereas the smaller, less hydrated and more polarizing anions have the greater tendency to reside at the particle surface. Surface-active agents, strongly adsorbed by the hydrophobic effect, will usually determine the surface charge when adsorbed.

The electrical double layer

Consider a solid charged surface in contact with an aqueous solution containing positive and negative ions. The surface charge influences the distribution of ions in the aqueous medium; ions, of opposite charge to that of the surface, termed counter ions, are attracted towards the surface, ions of like charge, termed co-ions, are repelled away from the surface. However, the distribution of the ions will also be affected by thermal agitation which will tend to redisperse the ions in solution. The result is the formation of an electric double layer made up of the charged surface and

a neutralizing excess of counter ions over co-ions (the system must be electrically neutral) distribution in a diffuse manner in the aqueous medium.

The theory of the electrical double layer deals with this distribution of ions and hence with the magnitude of the electric potentials which occur in the locality of the charged surface. For a fuller explanation of what is a rather complicated mathematical approach the reader is referred to a textbook of colloid science (e.g. Shaw, 1980). A somewhat simplified picture of what pertains from the theories of Gouy, Chapman and Stern follows.

The double layer is divided into two parts (see Fig. 6.1(a)), the inner, which may include adsorbed ions, and the diffuse part where ions are distributed as influenced by electrical forces and random thermal motion. The two parts of the double layer are separated by a plane, the Stern plane, at about a hydrated ion radius from the surface, thus counter ions may be held at the surface by electrostatic attraction and the centre of these hydrated ions forms the Stern plane.

The potential changes linearly from ψ_0 (the surface potential) to ψ_δ (the Stern potential) in the Stern layer and decays exponentially from ψ_δ to zero in the diffuse double layer (Fig. 6.1(b)). A plane of shear is also indicated in Fig. 6.1(a) and (b). In addition to ions in the Stern layer a certain amount of solvent will be bound to the ions and the charged surface. This solvating layer is held to the surface and the edge of the layer, termed the surface or plane of shear, represents the boundary of relative movement between the solid (and attached material) and the liquid. The potential at the plane of shear is termed the zeta, ζ, or electrokinetic, potential and its magnitude may be measured using microelectrophoresis or any other of the electrokinetic phenomena. The thickness of the solvating layer is ill-defined and the zeta potential therefore represents a potential at an unknown distance from the particle surface; its value, however, is usually taken as being slightly less than that of the Stern potential.

In the discussion above it was stated that the Stern plane existed at an hydrated ion radius from the particle surface; the hydrated ions are electrostatically attracted to the particle surface. It is possible for ions/molecules to be more strongly adsorbed at the surface — termed specific adsorption — than simple electrostatic attraction. In fact the specifically adsorbed ion/molecule may be uncharged as in the case with non-ionic surface-active agents. Surface-active ions specifically

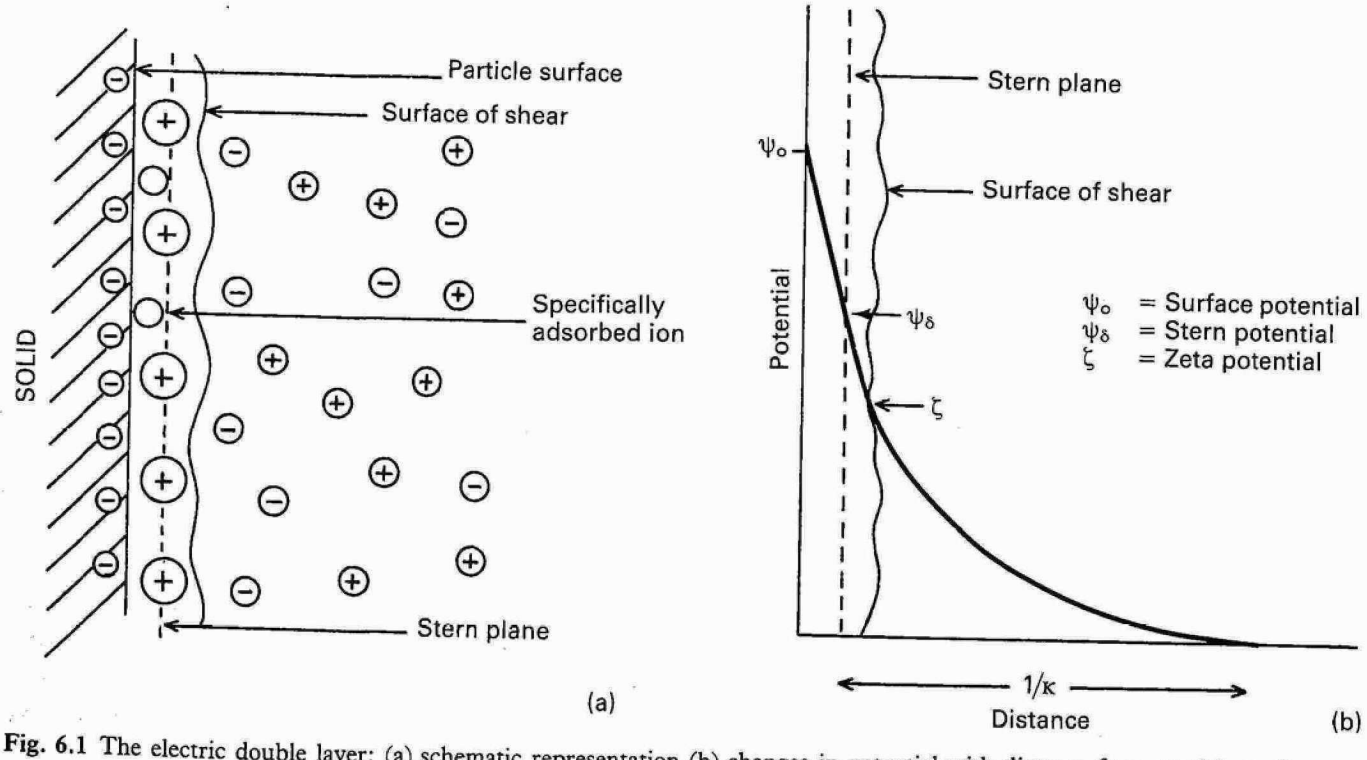


Fig. 6.1 The electric double layer: (a) schematic representation (b) changes in potential with distance from particle surface

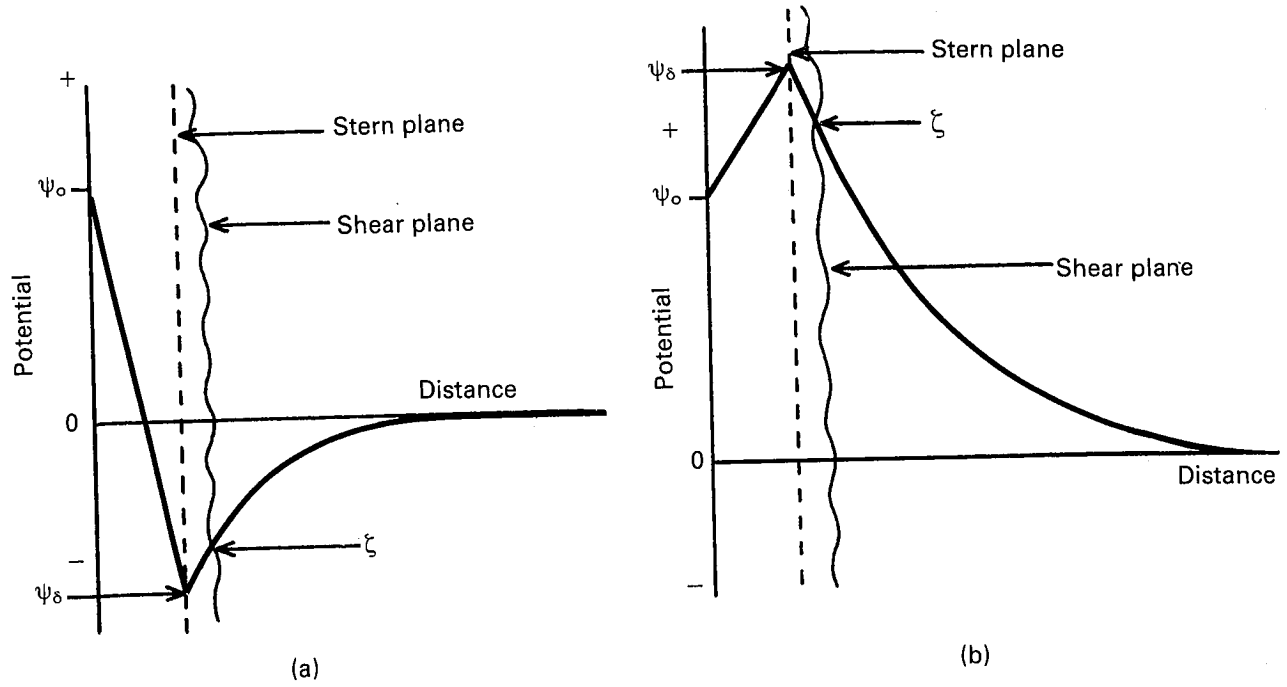


Fig. 6.2 Changes in potential with distance from solid surface: (a) reversal of charge sign of Stern potential ψ_δ, due to adsorption of surface-active or polyvalent counter ion, (b) increase in magnitude of Stern potential ψ_δ, due to adsorption of surface active co-ions

adsorb by the hydrophobic effect and can have a significant effect on the Stern potential causing ψ_0 and ψ_δ to have opposite signs as in Fig. 6.2(a) or for ψ_δ to have the same sign as ψ_0 but be greater in magnitude Fig. 6.2(b).

In Fig. 6.1(b) it is shown that the potential decays exponentially to zero with distance from the Stern plane, and the distance over which this occurs is $1/\kappa$, the Debye–Huckel length parameter known as the thickness of the electrical double layer. The parameter κ is dependent on the electrolyte concentration of the aqueous media (see Shaw, 1980 for details).

Increasing the electrolyte concentration means therefore that one is increasing the value of κ and consequently decreasing the value of $1/\kappa$, the thickness of the double layer, or as it is said one is 'compressing the double layer'; or the distance over which the potential decays exponentially is reduced. As ψ_δ stays constant this means that the zeta potential will be lowered.

As indicated earlier the effect of specifically adsorbed ions may be to lower the Stern potential and hence the zeta potential without compressing the double layer. Thus the zeta potential may be reduced by additives to the aqueous system in either (or both) of two different ways.

Electrokinetic phenomena

This is the general description applied to the phenomena which arise when attempts are made to shear off the mobile part of the electrical double layer from a charged surface. There are four such phenomena, namely, electrophoresis, sedimentation potential, streaming potential and electroosmosis. All of these electrokinetic phenomena may be used to measure the zeta potential but electrophoresis is the easiest to use and has the greatest pharmaceutical application.

Electrophoresis The movement of a charged particle (plus attached ions) relative to a stationary liquid under the influence of an applied electric field is termed electrophoresis. When the movement of the particles is observed with a microscope, or the movement of light spots scattered by particles too small to be observed with the microscope is observed using an ultramicroscope, this constitutes microelectrophoresis.

A microscope equipped with an eye piece graticule is used and the speed of movement of the particle under the influence of a known electric field is measured. This is the electrophoretic velocity, v, and the electrophoretic mobility, u, is given by

$$u = v/E \qquad (6.21)$$

where v is measured in m s^{-1}, and E, the applied field strength in V m^{-1}, so that u has the dimensions of m^2 s^{-1} V^{-1}. Typically a stable lyophobic colloidal particle may have an electrophoretic mobility of 4×10^{-8} m^2 s^{-1} V^{-1}. The equation used for converting the electrophoretic mobility, u, into the zeta potential depends on the value of κa (κ is the Debye–Huckel reciprocal length parameter described previously and a the particle radius). For values of $\kappa a > 100$ (as is the case for particles of radius 1 μm dispersed in 10^{-3} mol dm^{-3} sodium chloride solution) the Smoluchowski equation can be used:

$$u = \varepsilon\zeta/\eta \qquad (6.22)$$

Where ε is the permittivity and η the viscosity of the liquid used. For particles in water at 25 °C, $\zeta = 12.85 \times 10^{-5}$ u volts. So that for the mobility given above a zeta potential of 0.0514 volts or 51.4 millivolts is obtained. For values of $\kappa a < 100$ as complicated relationship which is a function of κa and the zeta potential is used (Wiersema *et al.*, 1966).

The technique of microelectrophoresis finds application in the measurement of zeta potentials, of model systems (like polystyrene latex dispersions) to test colloid stability theory, of course dispersions (like suspensions and emulsions) to assess their stability, and in identification of charge groups and other surface characteristics of water-insoluble drugs and cells such as blood and bacteria.

Other electrokinetic phenomena The other electrokinetic phenomena are as follows: *sedimentation potential*, the reverse of electrophoresis, is the electric field created when particles sediment; *streaming potential*, the electric field created when liquid is made to flow along a stationary charged surface, e.g. a glass tube or a packed powder bed; and *electro-osmosis*, the opposite of streaming potential, the movement of liquid relative to a stationary charged surface, e.g. a glass tube, by an applied electric field.

Physical stability of colloidal systems

In colloidal dispersions, frequent encounters between the particles occur due to Brownian movement. Whether these collisions result in permanent contact of the particles (coagulation), when eventually the colloidal system will be destroyed as the large aggregates formed sediment out, or temporary contact (flocculation), or whether the particles rebound and remain freely dispersed (a stable colloidal system) depends on the forces of interaction between the particles. These forces can be divided into three groups: electrical forces of repulsion, forces of attraction and forces arising from solvation. An understanding of the first two explains the stability of lyophobic systems and all three lyophilic dispersions. Before considering the interaction of these forces it is necessary to define the terms *aggregation*, *coagulation* and *flocculation* as used in colloid science.

Aggregation is a general term signifying the collection of particles into groups.

Coagulation, from the latin coagulare, meaning to drive together, to compact, signifies that the particles are closely aggregated and difficult to redisperse — a primary minimum phenomenon of the DLVO theory of colloid stability (see next section).

Flocculation comes from the latin flocculare, meaning loose and woolly. Aggregates have an open structure in which the particles remain a small distance apart from one another. This may be a secondary minimum phenomenon (see the DLVO theory) or due to bridging by a polymer or polyelectrolyte as explained later in this section.

As a preliminary to discussion on the stability of colloidal dispersions a comparison of the general properties of lyophobic and lyophilic sols is given in Table 6.2.

Stability of lyophobic systems

DLVO theory In considering the interaction between two colloidal particles Derjaguin and Landau and independently, Verwey and Overbeek, in the 1940s produced a quantitative approach to the stability of hydrophobic sols. In what has come to be known as the *DLVO theory of colloid stability* they assumed that the only interactions involved are electrical repulsion, V_R, and van der Waals attraction, V_A, and that these parameters are additive. Therefore the total poten-

Table 6.2 Comparison of properties of lyophobic and lyophilic sols

Property	*Lyophobic*	*Lyophilic*
Effect of electrolytes	Very sensitive to added electrolyte leading to aggregation in an irreversible manner. Depends on: (a) type and valency of counter ion of electrolyte, e.g. with a negatively charged sol, $La^{3+} > Ba^{2+} > Na^{+}$. (b) Concentration of electrolyte. At a particular concentration sol passes from disperse to aggregated state. For the electrolyte types in (a) the concentrations are about 10^{-4}; 10^{-3}; 10^{-1} mol dm^{-3} respectively. These generalizations, (a) and (b), form what is known as the Schulze–Hardy rule	Dispersions are stable generally in the presence of electrolytes. May be salted out by high concentrations of very soluble electrolytes. Effect is due to desolvation of the lyophilic molecules and depends on the tendency of the electrolyte ions to become hydrated. Proteins more sensitive to electrolytes at their isoelectric points. Lyophilic colloids when salted out may appear as amorphous droplets known as a coacervate
Stability	Controlled by charge on particles	Controlled by charge and solvation of particles
Formation of dispersion	Dispersions usually of metals, inorganic crystals etc., with a high interfacial surface-free energy due to large increase in surface area on formation. A positive ΔG of formation, dispersion will never form spontaneously and is thermodynamically unstable. Particles of sol remain dispersed due to electrical repulsion	Generally proteins, macromolecules etc., which disperse spontaneously in a solvent. Interfacial free energy is low. There is a large increase in entropy when rigidly held chains of a polymer in the dry state unfold in solution. The free energy of formation is negative, a stable thermodynamic system.
Viscosity	Sols of low viscosity, particles unsolvated and usually symmetrical	Usually high, at sufficiently high concentration of disperse phase a gel may be formed. Particles solvated and usually asymmetric

tial energy of interaction V_T (expressed schematically in the curve shown in Fig. 6.3) is given by

$$V_T = V_A + V_R \qquad (6.23)$$

Repulsive forces between particles Repulsion between particles arises due to the osmotic effect produced by the increase in the number of charged species on overlap of the diffuse parts of

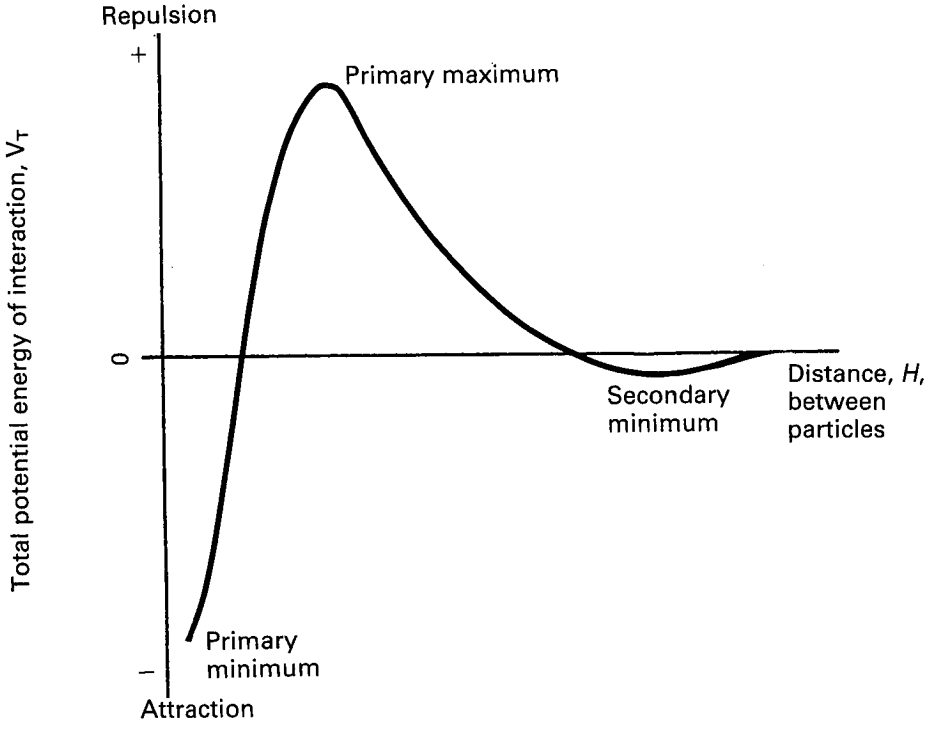


Fig. 6.3 Schematic curve of total potential energy of interaction V_T, versus distance of separation, H, for two particles. $V_T = V_R + V_A$

the electrical double layer. No simple equations can be given for repulsive interactions; however, it can be shown that the repulsive energy that exists between two spheres of equal but small surface potential is given by:

$$V_R = \frac{\varepsilon a \psi_0^2 \ln(1 + \exp^{-\kappa H})}{2} \qquad (6.24)$$

where ε is the permittivity of the polar liquid, a the radius of the spherical particle of surface potential ψ_0, κ is the Debye–Huckel reciprocal length parameter and H the distance between particles. An estimation of the surface potential can be obtained from zeta potential measurements. As can be seen the repulsion energy is an exponential function of the distance between the particles and has a range of the order of the thickness of the double layer.

Attractive forces between particles The energy of attraction, V_A, arises from van der Waals universal forces of attraction, the so-called dispersion forces, the major contribution to which are the electromagnetic attractions described by London in 1930. For an assembly of molecules dispersion forces are additive summation leading to long range attraction between colloidal particles. As a result of the work of de Boer and Hamaker in 1936 it can be shown that the attractive interaction between spheres of the same radius, a, is given by:

$$V_A = \frac{-Aa}{12H} \qquad (6.25)$$

where A is the Hamaker constant for the particular material derived from London dispersion forces. The energy of attraction varies as the inverse of the distance between particles.

Total potential energy of interaction Consideration of the curve, total potential energy of interaction V_T, versus distance between particles, H, Fig. 6.3, shows that attraction predominates at small distances, hence the very deep primary minimum, and at large interparticle distances. Here the secondary minimum arises because the fall off in repulsive energy with distance is more rapid than that of attractive energy. At intermediate distances double layer repulsion may predominate giving a primary maximum in the curve, if this maximum is large compared with the thermal energy kT of the particles the colloidal system should be stable, i.e. the particles stay dispersed. Otherwise the interacting particles will reach the energy depth of the primary minimum and irreversible aggregation, i.e., coagulation occurs. If the secondary minimum is smaller than kT the particles will not aggregate but will always repel one another, but if significantly larger than kT a loose assemblage of particles will form which can be easily redispersed by shaking, i.e. flocculation occurs.

The depth of the secondary minimum depends on particle size and particles may need to be of radius 1 μm or greater before the attractive force is sufficiently great for flocculation to occur.

The height of the primary maximum energy barrier to coagulation depends upon the magnitude of V_R, which is dependent on ψ_O and hence the zeta potential and in addition on electrolyte concentration via κ, the Debye–Huckel reciprocal length parameter. Addition of electrolyte compresses the double layer and reduces the zeta potential: this has the effect of lowering the primary maximum and deepening the secondary minimum (see Fig. 6.4). This latter means that there will be an increased tendency for particles to flocculate in the secondary minimum and is the principle of the *controlled flocculation* approach to pharmaceutical suspension formulation described later.

The primary maximum may also be lowered (and the secondary minimum deepened) by adding substances, such as ionic surface-active agents, which are specifically adsorbed within the Stern layer. Here ψ_δ is reduced and hence the zeta potential; the double layer is usually not compressed.

Stability of lyophilic systems

Solutions of macromolecules, lyophilic colloidal sols, are stabilized by a combination of electrical double layer interaction and solvation and both of these stabilizing factors must be sufficiently weakened before attraction predominates and the colloidal particles coagulate. For example gelatin has a sufficiently strong affinity for water to be soluble even at its isoelectric pH where there is no double layer interaction.

Hydrophilic colloids are unaffected by the small

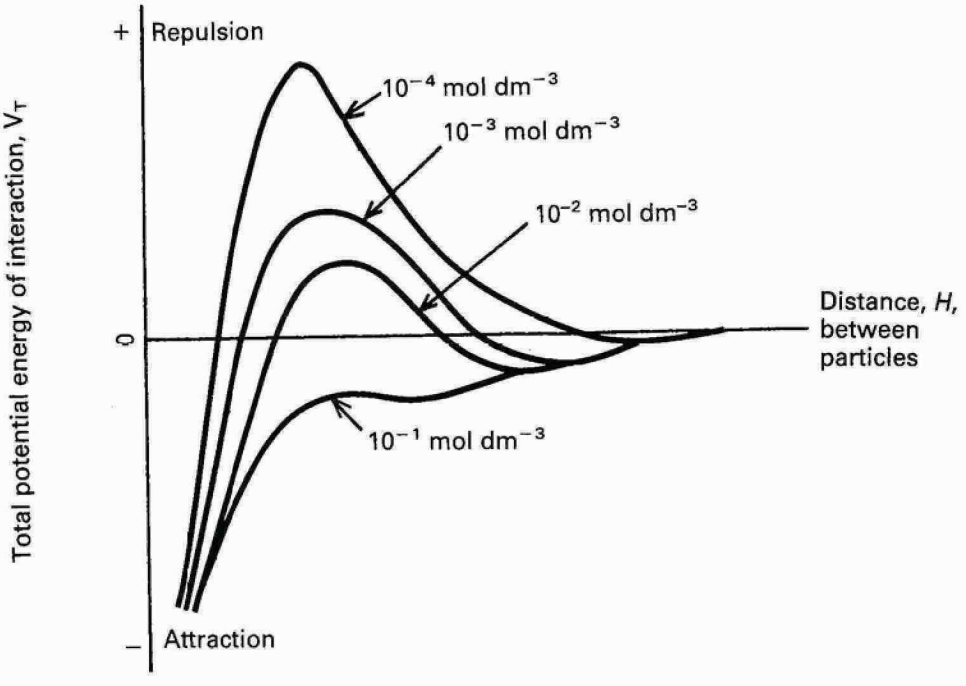


Fig. 6.4 Schematic curves of total potential energy of interaction V_T, versus distance of separation, H, showing the effect of adding electrolyte at constant surface potential

amounts of added electrolyte which cause hydrophobic sols to coagulate; however, when the concentration of electrolyte is high, particularly with an electrolyte whose ions become strongly hydrated, the colloidal material loses its water of solvation to these ions and coagulates, i.e. a 'salting out' effect occurs.

Variation in the degree of solvation of different hydrophilic colloids affects the concentration of soluble electrolyte required to produce their coagulation and precipitation. The components of a mixture of hydrophilic colloids can therefore be separated by a process of fractional precipitation, which involves the 'salting' out of the various components at different concentrations of electrolyte. This technique is used in the purification of antitoxins.

Lyophilic colloids can be considered to become lyophobic by the addition of solvents such as acetone and alcohol. The particles become desolvated and are then very sensitive to precipitation by added electrolyte.

Coacervation and microencapsulation Coacervation is the separation from a lyophilic sol, on addition of another substance, of a colloid-rich layer present in the form of an amorphous liquid. This constitutes the coacervate.

Simple coacervation may be brought about by a 'salting out' effect on addition of electrolyte or addition of a non-solvent. Complex coacervation occurs when two oppositely charged lyophilic colloids are mixed, e.g. gelatin and acacia. Gelatin at a pH below its isoelectric point is positively charged, acacia above about pH 3 negatively charged; a combination of solutions at about pH 4 results in coacervation. Any large ions of opposite charge, for example cationic surface-active agents (positively charged) and dyes used for colouring aqueous mixtures (negatively charged), may react in a similar way.

If the coacervate is formed in a stirred suspension of an insoluble solid the macromolecular material will surround the solid particles. The coated particles can be separated and dried and this technique forms the basic of one method of microencapsulation. A number of drugs including aspirin have been coated in this manner. The coating protects the drug from chemical attack and microcapsules may be given orally to prolong the action of the medicament.

Effect of addition of macromolecular material to lyophobic colloidal sols When added in small amounts many polyelectrolyte and polymer molecules (lyophilic colloids) can adsorb simul-

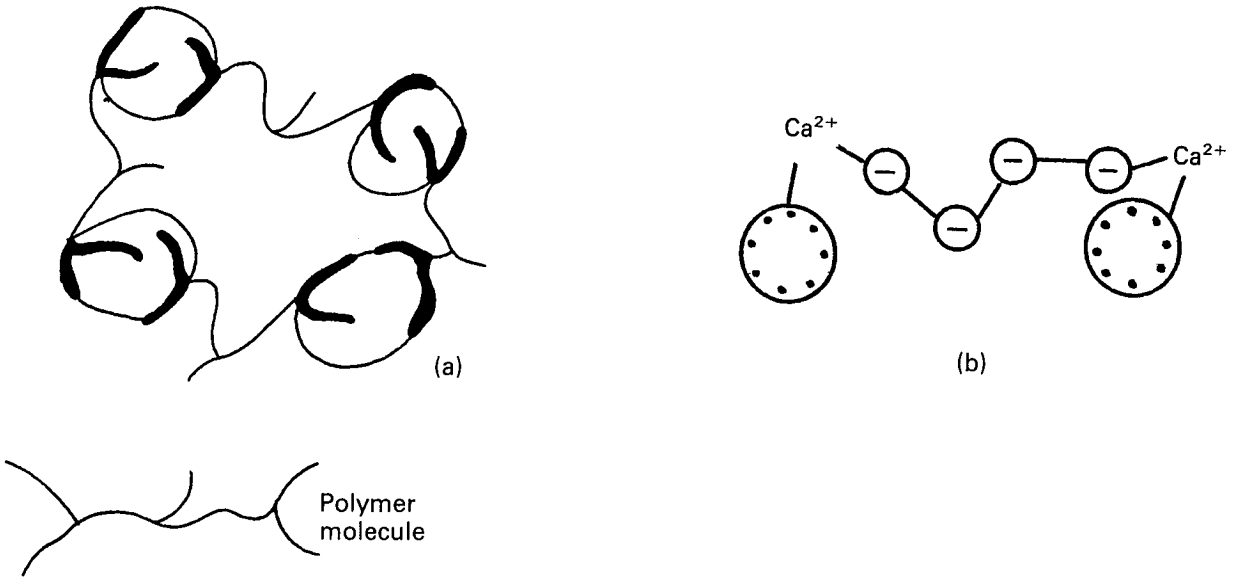


Fig. 6.5 Diagram of flocs formed (a) by polymer bridging and (b) polyelectrolyte bridging in the presence of divalent ions of opposite charge

taneously on to two particles and are long enough to bridge across the energy barrier between the particles. This can even occur with neutral polymers when the lyophobic particles have a high zeta potential (and would thus be considered a stable sol). A structured floc results (Fig. 6.5(a)).

With polyelectrolytes, where the particles and polyelectrolyte have the same sign, flocculation can often occur when divalent and trivalent ions are added to the system (Fig. 6.5(b)). These complete the 'bridge' and only very low concentrations of these ions are needed. Use is made of this property of small quantities of polyelectrolytes and polymers in removing colloidal material, resulting from sewage, in water purification.

On the other hand if larger amounts of polymer are added, sufficient to cover the surface of the particles, then a lyophobic sol may be stabilized to coagulation by added electrolyte — the so-called steric stabilization or protective colloid effect.

Steric stabilization (protective colloid action)

It has been known for a long time that non-ionic polymeric material such as gums, non-ionic surface-active agents and methylcellulose adsorbed at the particle surface can stabilize a lyophobic sol to coagulation even in the absence of a significant zeta potential. The approach of two particles, with adsorbed polymer layers, results in a steric interaction when the layers overlap leading to repulsion. In general the particles do not approach each other closer than about twice the thickness of the adsorbed layer and hence passage into the primary minimum is inhibited. An additional term has thus to be included in the potential energy of interaction for what is called steric stabilization, V_S, the older term being protective colloid action:

$$V_T = V_A + V_R + V_S \qquad (6.26)$$

The effect of V_S on the potential energy against distance between particles curve is seen in Fig. 6.6, showing that repulsion is generally seen at all shorter distances provided that the adsorbed polymeric material does not move from the particle surface.

One can explain steric repulsion by reference to the free energy changes which take place when two polymer covered particles interact. Free energy, enthalpy and entropy changes are related according to the Gibbs–Helmholtz equation:

$$\Delta G = \Delta H - T\Delta S \qquad (6.27)$$

The second law of thermodynamic implies that a positive value of ΔG is necessary for dispersion stability, a negative value indicating that the particles have aggregated.

A positive value of ΔG can arise in a number of ways, as when ΔH and ΔS are both negative

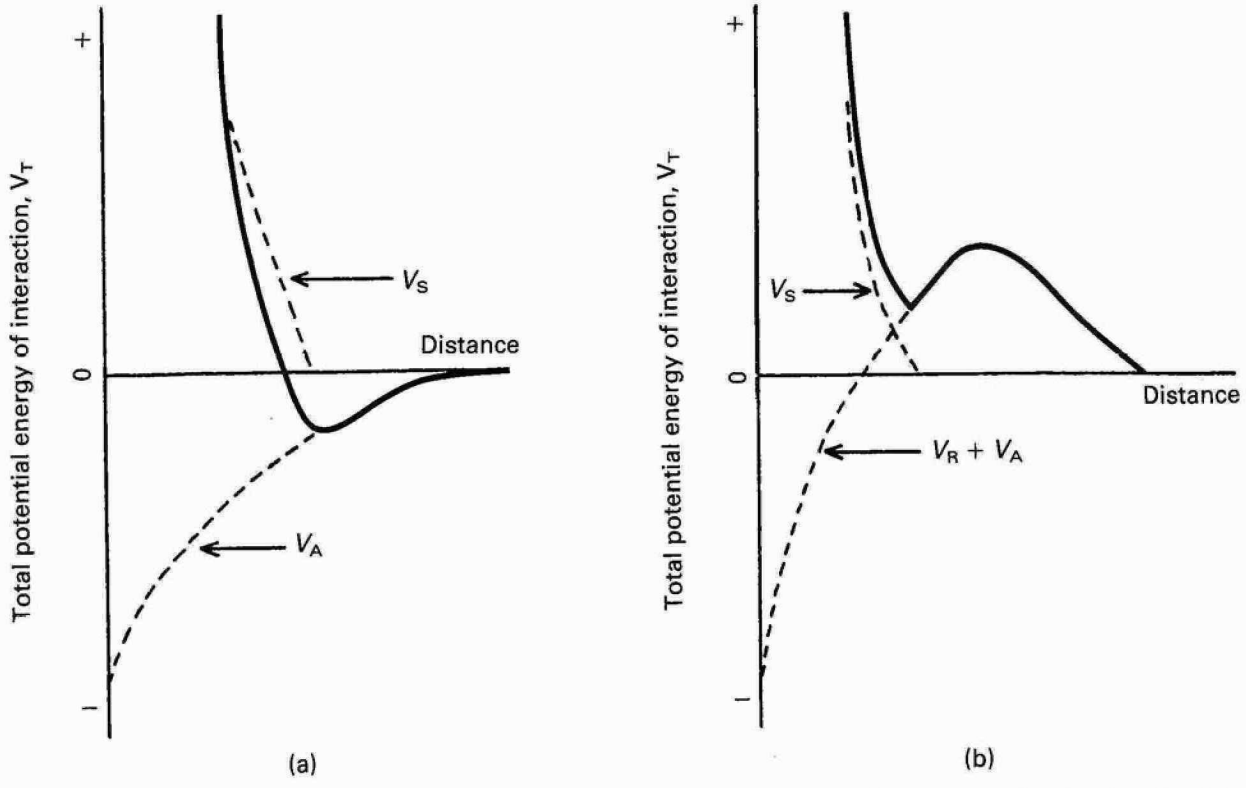


Fig. 6.6 Schematic curves of the total potential energy of interaction versus distance for two particles, showing the effect of the steric stabilization term V_S: (a) in the absence of electrostatic repulsion, the solid line representing $V_T = V_A + V_S$, (b) in the presence of electrostatic repulsion, the solid line representing $V_T = V_R + V_A + V_s$

but $T\Delta S > \Delta H$. Here the effect of the entropy change opposes aggregation and outweighs the enthalpy term; this is termed *entropic stabilization*. Interpenetration and compression of the polymer chains decreases the entropy as these chains become more ordered. Such a process is not spontaneous: 'work' must be expended to interpenetrate and compress any polymer chains existing between the colloidal particles and this work is a reflection of the repulsive potential energy. The enthalpy of mixing of these polymer chains will also be negative. Stabilization by these effects occurs in non-aqueous dispersions.

Again, a positive ΔG occurs if both ΔH and ΔS are positive but $\Delta H > T\Delta S$. Here enthalpy aids stabilization, entropy aids aggregation. Consequently this effect is termed enthalpic stabilization and is common with aqueous dispersions, particularly where the stabilizing polymer has polyoxyethylene chains. Such chains are hydrated in aqueous solution due to H-bonding between water molecules and the 'ether oxygens' of the ethylene oxide groups. The water molecules have thus become more structured and

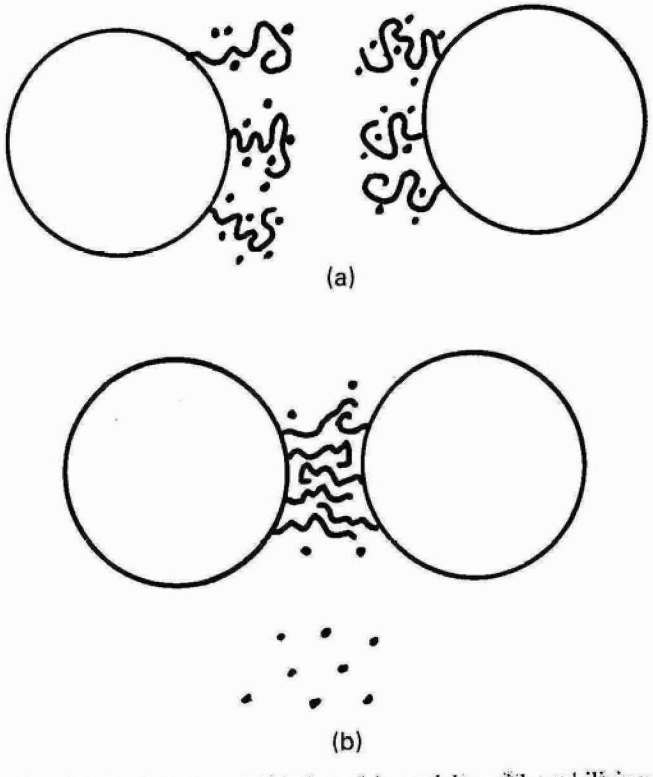


Fig. 6.7 Enthalpic stabilization: (a) particles with stabilizing polyoxyethylene chains and H-bonded water molecules, (b) stabilizing chains overlap, water molecules released. $\rightarrow + \Delta H$

lost degrees of freedom. When interpenetration and compression of ethylene oxide chains occurs there is an increased probability of contact between ethylene oxide groups resulting in some of the bound water molecules being released (see Fig. 6.7). The released water molecules have greater degrees of freedom than those in the bound state. For this to occur they must be supplied with energy, obtained from heat absorption, i.e. there is a positive enthalpy change. Although there is a decrease in entropy in the interaction zone as with entropic stabilization this is over-ridden by the increase in the configurational entropy of the released water molecules.

GELS

The majority of gels are formed by aggregation of colloidal sol particles, the solid or semisolid system so formed being interpenetrated by a liquid. The particles link together to form an interlaced network thus imparting rigidity to the structure, the continuous phase is held within the meshes. This type of structure is supported by the fact that only a small percentage of disperse phase is required to impart rigidity, for example 1% of agar in water produces a firm gel. Further, diffusion of non-electrolytes in, and the electrical conductivity of, dilute gels are the same as the continous phase.

A gel rich in liquid may be called a jelly; if the liquid is removed and only the gel framework remains this is termed a xerogel. Sheet gelatin, acacia tears and tragacanth flakes are all xerogels.

Types of gel

Gels may be flocculated lyophobic sols where the gel can be looked upon as a continuous floccule (Fig. 6.8(a)). Examples are aluminium hydroxide and magnesium hydroxide gels.

Clays such as bentonite, aluminium magnesium silicate (Veegum) and to some extent kaolin form gels by flocculation in a special manner. Only a simplified general explanation of gel formation by clays can be given. They are hydrated aluminium (aluminium/magnesium) silicates whose crystal

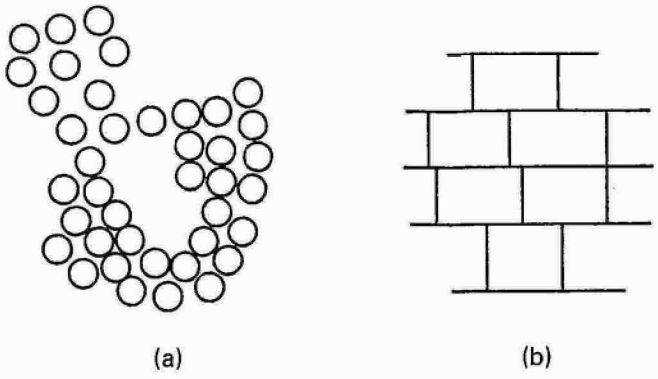


Fig. 6.8 Gel structure: (a) flocculated lyophobic sol, e.g. aluminium hydroxide, (b) 'card house' floc of clays, e.g. bentonite

structure is such that they exist as flat plates, the flat part or 'face' of the particle carries a negative charge due to 0^- atoms and the edge of the plate a positive charge due to Al^{3+}/Mg^{2+} atoms. As a result of electrostatic attraction between the face and edge of different particles a gel structure is built up, forming what is usually known as a 'card house floc' (Fig. 6.8(b)).

The forces holding the particles together in this type of gel are relatively weak — van der Waals forces in the secondary minimum flocculation of aluminium hydroxide, electrostatic attraction in the case of the clays — because of this these gels show the phenomenon of *thixotropy*, a non-chemical isothermal gel–sol–gel transformation. If a thixotropic gel is sheared (for example by simple shaking) these weak bonds are broken and a lyophobic sol is formed. On standing the particles collide, flocculation occurs and the gel is reformed. Flocculation in gels is the reason for their anomalous rheological properties (Chapter 2). This phenomenon of thixotropy is made use of in formulation of pharmaceutical suspensions, e.g. bentonite in calamine lotion and in the paint industry.

On the other hand lyophilic sols form gels in a different manner. The macromolecules may form a network simply by entanglement. e.g. tragacanth and methylcellulose, or by attraction between molecules such as hydrogen bonds or van der Waal's forces. An increase in temperature often breaks these weak bonds causing liquefaction of the gel. Systems that exhibit this type of transition such as agar and gelatin gels, are

termed thermal gels. Gels often contract spontaneously and exude some of the fluid medium. This effect is known as *syneresis* and is thought to be due to an increase in the number of bonding points, resulting in a coarsening of the matrix structure and consequent expression of liquid from the gel.

The cross-binding of macromolecules by primary valency bonds provides a further mechanism for the formation of a gel network and here the gelling process is irreversible. This behaviour is exhibited by silica gel where silicic acid molecules are linked into a three-dimensional network by Si–O bonds. Silica gel has a great affinity for water and is used as a drying agent.

Applications

Mineral oils may be gelled by warming with the insoluble soap aluminium monostearate. Heat energy appears necessary for the molecules to orientate themselves into a gel structure. Such gels are used to suspend medicaments in oily injections. Liquid paraffin gelled similarly with polythene forms a proprietary ointment base. Other organic liquids may be gelled with aluminium monostearate and this forms the basis of a method of preparation of a slow release medicament. Particles of drug are suspended in a volatile solvent, aluminium monostearate is added and the mixture warmed to produce a gel the matrix of which enmeshes the drug particles. The solvent is then evaporated and the dry gel broken up into granules which contain particles of the drug suitable for tablet making. The gel particles provide water resistant barriers on exposure to the fluid of the gastrointestinal tract and hence slow the release of the drug.

SURFACE-ACTIVE AGENTS

Surface-active agents, or surfactants, are substances that alter the conditions prevailing at an interface, causing, for example, a marked decrease in the surface tension of water. These substances are of importance in a wide variety of fields as emulsifying agents, detergents, solubilizing agents, wetting agents, foaming and antifoaming agents, flocculants and deflocculants, and in drug stability and drug absorption.

All surfactants are characterized by having two regions in their molecular structure:

1 a lyophobic (or hydrophobic) group, such as a hydrocarbon chain, that has no affinity for aqueous solvents, and
2 a lyophilic (or hydrophilic) group that has an affinity for water.

To have such an affinity the group must possess an appreciable polar character, e.g. an ion or group with a large permanent dipole. A molecule or ion that possesses this type of structure is termed amphipathic.

Surface-active agents may be classified according to the nature of the ionic type of the hydrophilic group and various examples of the different classes are shown in Table 6.3.

A wide variety of drugs have also been reported to be surface active, this surface activity being a consequence of the amphipathic nature of the drugs. The hydrophobic portions of the drug molecules are usually more complex than those of the surface-active agents described being composed of aromatic or heterocyclic ring systems. Examples include drugs such as chlorpromazine and imipramine which have tricyclic ring systems; diphenhydramine and orphenadrine which are based on a diphenylmethane group; and tetrocaine and mepyramine which have a hydrophobic group composed of a single phenyl ring.

The dual nature of the structure possessed by surfactants is responsible for their characteristic properties. Thus in dilute aqueous solution the molecules tend to orientate themselves at the air/water interface in such a way as to remove the hydrophobic group from the aqueous phase, and hence achieve a minimum free energy state. However, at certain well defined concentrations, specific for any surfactant and depending on structural characteristics, relatively sharp changes occur in the physical properties of these solutions. These changes are attributed to the association of the amphipathic molecules into aggregates of colloidal dimensions known as micelles.

Ionic and non-ionic substances that exhibit this

Table 6.3 Classification of surface-active agents

	Hydrophobic	*Hydrophilic*
Anionic		
Sodium dodecanoate	$CH_3(CH_2)_{10}$	COO^-Na^+
Sodium dodecyl (lauryl) sulphate	$CH_3(CH_2)_{11}$	$SO_4^-Na^+$
Sodium dioctyl sulphosuccinate	$CH_3(CH_2)_7.OOC.CHSO_3^-Na^+$	$CH_3(CH_2)_7.OOC.CH_2$
Cationic		
Hexadecyl trimethyl ammonium bromide (Cetrimide)	$CH_3(CH_2)_{15}$	$N^+(CH_3)_3Br^-$
Dodecyl pyridinium iodide	$CH_3(CH_2)_{11}$	N^+Br^-
Non-ionic		
Hexaoxyethylene monohexadecyl ether	$CH_3(CH_2)_{15}$	$(OCH_2CH_2)_6OH$
Polyoxyethylene sorbitan mono-oleate (polysorbate 80)	$C_{17}H_{33}$	$COO-CH_2$ $HO(OCH_2CH_2)_n$ $(CH_2CH_2O)_nOH$ $(CH_2CH_2O)_nOH$
Sorbitan mono-oleate	$C_{17}H_{33}$	$COOCH_2$ HO, OH, OH
Ampholytic *N*-dodecyl alanine	$CH_3(CH_2)_{11}$	$NH_2^+.CH_2.CH_2.COO^-$
Lecithin	$C_{17}H_{35}$ $C_{17}H_{35}$	$COO.CH_2$ $COO.CH$ $CH_2-O-P(=O)(O^-).(CH_2)_3.N^+(CH_3)_3$

type of behaviour are referred to collectively as *association colloids*. Although the older term 'colloidal electrolyte' is strictly applicable to all ionized colloidal materials it is usually reserved for ionic association colloids. Since the early work in this field was carried out solely on ionic association colloids the term 'colloidal electrolyte' is still sometimes used erroneously as a synonym for all association colloids.

Micellization

As mentioned earlier surfactants in dilute aqueous solution orientate themselves at the air/water interface but, as the concentration of surfactant increases the molecules also aggregate together to form micelles. The primary reason that this occurs is the attainment of a state of minimum free energy. The free energy, enthalpy and entropy changes in a system are related by

$$\Delta G = \Delta H - T\Delta S$$

and, for surfactant solution systems, the entropy term is by far the most important in determining free energy changes.

The explanation most generally accepted for the entropy change is concerned with the structure of water. Water possesses a relatively high degree of structure due to hydrogen bonding between adjacent molecules. If an ionic or strongly polar solute

is added to water it will disrupt this structure but the solute molecules can form hydrogen bonds with the water molecules which more than compensates for the disruption or distortion of the bonds existing in pure water. Ionic and polar materials thus tend to be easily soluble in water. No such compensation occurs with non-polar groups and their solution in water is accordingly resisted, the water molecules forming extra structured clusters around the non-polar region. This increase in structure of the water molecules leads to a negative entropy change and results in the withdrawal of the hydrophobic groups from the water. Surface-active agents, because of their dual hydrophilic/hydrophobic structure, should and do have a measurable solubility in water depending on whether or not the polar group with its hydrogen bonding to the water molecules is sufficient to overcome the repulsive effect of the water molecules around the hydrophobic group.

From a thermodynamic point of view, however, the outstanding feature of the process of dissolving a surface-active agent in water is this large negative entropy change which is intimately related to the structuring of water around the hydrophobic portion of the molecule. To counteract this, and achieve a state of minimum free energy, the hydrophobic groups tend to withdraw from the aqueous phase. This may occur by the molecules orientating themselves at the interface with the hydrocarbon chain away from the aqueous phase, i.e., the molecules collect at air/water, oil/water and solid/water interfaces. However, as the concentration is increased, this method of free energy reduction becomes inadequate, and at a certain concentration, the *critical micelle concentration* (abbreviated CMC), the surfactant molecules may also achieve segregation of their hydrophobic portions from the solvent by self-aggregation. These aggregates are *micelles*. When the hydrophobic part of the surface-active agent is a hydrocarbon chain the micelles will consist of a hydrocarbon core with polar groups at the surface serving to maintain solubility in water.

This tendency for hydrophobic materials to be removed from water due to the strong attraction of water molecules for each other and not for the hydrophobic solute, has been termed hydrophobic bonding. However, because there is in fact no actual bonding between the hydrophobic groups the phenomenon is best described as the hydrophobic effect.

As the hydrophobic effect is due to the entropy changes associated with the structuring of water molecules around the hydrophobic group of the surface-active molecule it follows that as the length of this group increases there will be a greater entropy increase when it leaves the aqueous phase, i.e. the longer the hydrocarbon chain of a surfactant the more energetically favourable it is for such a molecule to be adsorbed at an interface or form a micelle.

There will be a similar entropy increase when a hydrocarbon chain is adsorbed at a solid hydrophobic surface, such as is present with many drugs. The same occurs at cell membranes, and it is not difficult to appreciate that surfactants can alter the characteristics of such membranes as bacterial cell walls or that of the gastrointestinal tract. Further, for exactly the same reasons, phospholipid molecules form themselves into layered structures, larger than micelles, termed liposomes.

Liposomes are liquid crystalline spherules formed when phospholipids are allowed to swell in aqueous media. They consist of concentric lipid bilayers alternating with aqueous compartments. The hydrocarbon chains are directed inwards in the structure away from the water for the same reason that micelles form. Lipid- and water-soluble substances can be trapped within the lipid or aqueous phase of the liposome respectively and give this structure possibilities as a drug delivery system.

An alternative explanation for the free energy decrease associated with micellization considers the increase in freedom of movement of the hydrocarbon chains, which occurs when these chains are transferred from the aqueous environment (where their movement is restrained by the structured water molecules) to the interior of the micelle, to be the important factor.

It should be emphasized that micelles are in dynamic equilibrium with monomer molecules in solution, continuously breaking down and reforming. It is this factor that distinguishes micelles from other colloidal particles and the reason why they are called association colloids.

The formation of micelles was originally

suggested by McBain in 1913 to explain the apparently anomalous changes in osmotic properties and electrical conductivity with concentration in solutions of potassium stearate. The osmotic activity and conductance were lower than expected as a certain concentration was reached. McBain's interpretation was for association of the molecules into large units called micelles but he postulated the existence of two types of micelle, one ionized and one neutral, to allow for the fall in conductivity.

Later, Hartley (1935) suggested that the experimental facts could be explained on the basis of a single type of spherical micelle composed of 50–100 units (see Fig. 6.9). Some counter ions will be attracted close to the micelle thus reducing the overall charge. The radius of the micelle will be slightly less than that of the extended hydrocarbon chain with the interior core of the micelle having the properties of a liquid hydrocarbon. He also postulated that once the CMC is reached further addition of material all goes to form micelles, that is, the concentration of monomeric surface-active agent remains constant above the CMC.

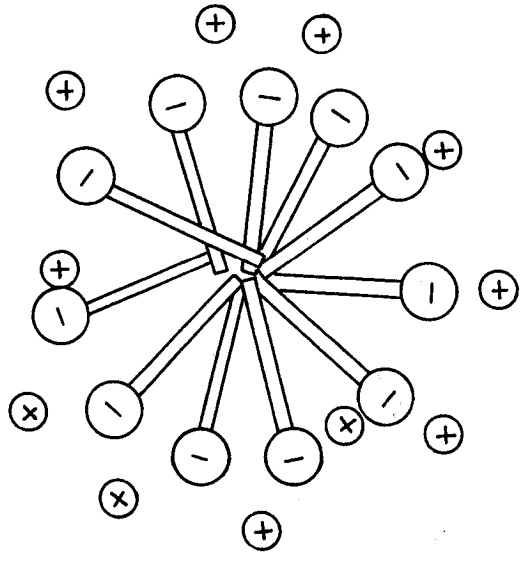


Fig. 6.9 Schematic diagram of the Hartley spherical micelle

The spherical micelle is now accepted as the most probable form existing in solutions above the CMC. However, as concentration is increased physical measurements, e.g. X-ray diffraction, viscosity, proton and deuterium magnetic resonance studies, indicate association of molecules in different ways forming cylindrical, lamellar and other structures.

With ionic surface-active agents repulsion between adjacent charged head groups tends to oppose micelle formation. It is for this reason that non-ionic surfactants form micelles at considerably lower concentrations.

Physical properties of surface-active agent solutions

Surface properties

Surface-active molecules in aqueous solution orientate themselves at the surface in such a way as to remove the hydrophobic group from the aqueous phase and hence achieve a minimum free energy state. As a result some of the water molecules at the surface are replaced by non-polar groups. The attractive forces between these groups and the water molecules, or between the groups themselves, are less than those existing between water molecules. The contracting power of the surface is thus reduced and so therefore is the surface tension. The adsorbed molecules can be looked upon as forming a bridge between the phases. The surface tension versus concentration curve for an aqueous solution of a surface-active agent thus shows a progressive decrease in surface tension until the CMC is reached. At this stage any additional surfactant goes to form micelles and the surface tension remains approximately constant beyond the CMC (Fig. 6.10). A minimum is frequently observed in the surface tension curve shown by the dotted curve in Fig. 6.10. Such minima are caused by the presence of surface-active impurities in the system, e.g. dodecanol present in sodium dodecyl (lauryl) sulphate. The initial adsorption into the surface layers of the surface-active agent of the impurity results in the lowering of the surface tension to a greater degree than that given by the pure surface-active agent. At the CMC the impurity is *solubilized* (see later in this chapter) by the micelles so that the surface tension rises to that of the pure surface-active agent beyond its CMC.

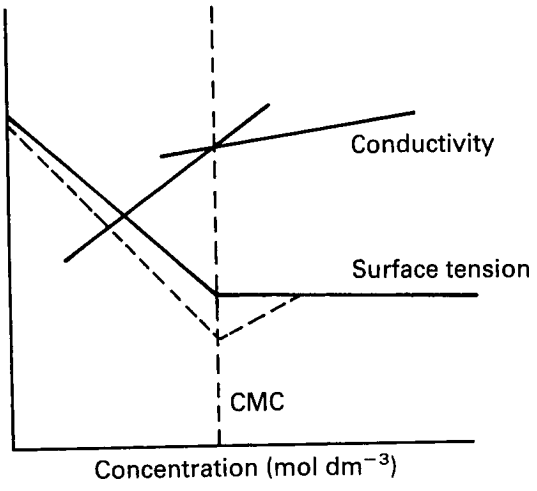


Fig. 6.10 Diagram of variation of conductivity and surface tension with concentration of an ionic surface-active agent such as sodium dodecyl sulphate

Electrical conductivity

The effect of micelle formation on the electrical conductivity of solutions of surface-active agents is also shown in Fig. 6.10. A number of factors contribute to the changes found.

The movement of ions towards an electrode is retarded by the viscous drag exerted on the charged particle by the solvent. There is actually a reduction in this viscous drag on micellization, e.g. a micelle formed of 100 monomers experiences less viscous drag than the total drag experienced by 100 individual monomers. The total charge on the micelle is the same as that of the constituent monomers so that this reduction in viscous drag should lead to increased conductance.

This, however, ignores the effect of the counter ions. First, the ionic atmosphere of opposite charge to the micelle exerts a braking effect due to relaxation (attraction between the charged micelle and the oppositely charged ions when these charged species move in opposite directions) and retardation (the counter ions, as they move, carry water molecules with them so that there is fluid flow counter to the movement of the micelle) effects. Second, due to the high charge and size of the micelle, some of the counter ions are bound to it, and move with it, thus travelling in a direction opposite to their normal direction of movement. These bound counter ions also reduce the effective charge on the micelle.

The counter ion effects cause a reduction in conductance and outweigh the reduction in viscous drag giving an overall fall of conductance on micellization. However, if a very high field strength is applied these counter ion effects can be removed and the expected increase in conductance occurs (the Wien effect).

Solubility; the Krafft point

The solubility behaviour of surface-active agents is anomalous in that as the temperature is increased a value is reached at which the material becomes highly soluble. If the CMC values for different temperatures are plotted on the same graph, it can be seen that at a particular temperature the solubility and CMC curves intersect. This temperature is the Krafft point and is characteristic for any particular surface-active agent. At temperatures below the Krafft point micelles will not form. It is therefore often necessary to use heat to get a surface-active agent into solution (the Krafft point for hexadecyltrimethyl ammonium bromide (cetrimide) is about 30 °C). Once the surface-active agent is in solution it may normally be cooled to room temperature without precipitation occurring.

Light scattering

The scattering of light by solutions of surface-active agents is increased by the aggregation of molecules into micelles. The slope of the graph of turbidity versus concentration therefore shows an abrupt increase at the CMC (Fig. 6.11(a)).

By use of Eqn 6.20 it is possible to obtain the micellar molecular weight and thus the number of monomer units forming the micelle.

Reference to Fig. 6.11(a) shows that the scattering due to micelles is $\tau - \tau_o$ whilst the concentration of surfactant present as micelles is $C - C_o$. Eqn 6.20 thus becomes

$$\frac{H(C - C_o)}{\tau - \tau_o} = 1/M_{\text{micelle}} + 2B(C - C_o) \qquad (6.28)$$

A plot of this equation (Fig. 6.11(b)) enables the micellar molecular weight to be evaluated.

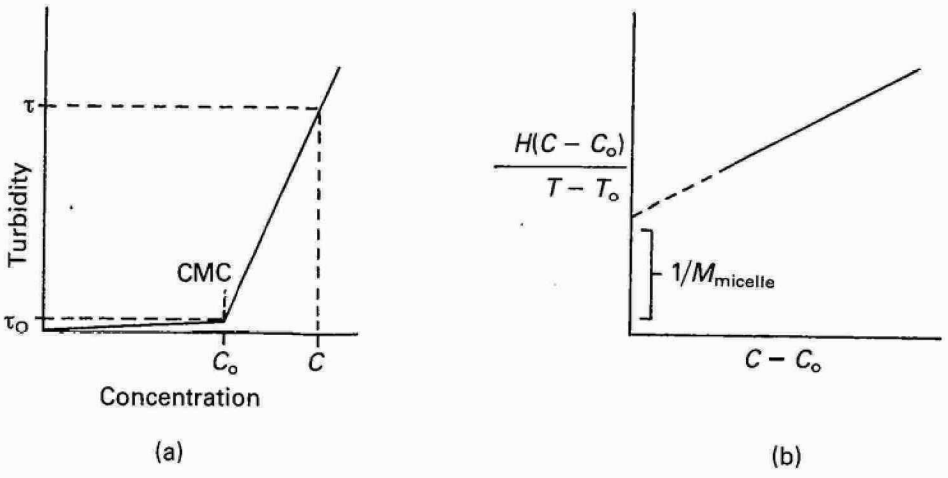


Fig. 6.11 Light scattering by solutions of surface-active agents: (a) turbidity versus concentration, (b) plot of the modified Debye equation for estimation of micellar size

Other methods of determining CMCs

Most physical properties change at the CMC and may be used to measure the magnitude of this concentration. At least 30 have been listed including, as well as those detailed above, all colligative properties, refractive index, viscosity and dye solubilization. In the latter case use is made of a solid dyestuff that is virtually insoluble in water, such as Orange OT. The amount of dyestuff in solution remains reasonably constant until the CMC is reached and then increases rapidly.

Solubilization

As mentioned previously the interior core of a micelle can be considered as having the properties of a liquid hydrocarbon and is thus capable of dissolving materials that are soluble in such liquids. This process whereby water-insoluble or partly soluble substances are brought into aqueous solution in quite high concentration is termed solubilization.

It was recognized early that the phenomenon of solubilization is connected in some way with the existence of micelles as solubilization does not occur until micelles are formed. Above the CMC the amount of substance solubilized (the solubilizate) increases as surfactant concentration increases, i.e. as the number of micelles increased.

The site of incorporation of the solubilizate is believed to be closely related to its chemical nature. Thus, it is generally accepted that non-polar solubilizates, e.g. aliphatic hydrocarbons, are dissolved in the hydrocarbon core of the micelle ((i) in Fig. 6.12(a)). Solubility of such a solubilizate should increase as the concentration of surface-active agent increases so that Hartley found that the solubility of *trans* azobenzene in the hydrocarbon interior of micelles of cetyl (hexadecyl) pyridinium chloride was quite close to its solubility in *n*-hexadecane. Water-insoluble compounds containing polar groups are orientated with the polar group at the surface of the ionic micelle amongst the micellar head groups and the hydrophobic group inside the hydrocarbon core of the micelle, the position of the molecule depending on the strength of the polar group, e.g. salicylic acid and naphthalene ((ii) and (iii) respectively in Fig. 6.12(a).

Solubilization in non-ionic polyoxyethylated surface-active agents can occur in the ethylene oxide shell which surrounds the core; thus *p*-hydroxy benzoic acid is entirely within this region hydrogen bonded to the ethylene oxide groups ((iv) in Fig. 6.12(b)) whilst esters such as the parabens are located at the shell core junction ((v) in Fig. 6.12(b)). Spectroscopic evidence for such orientations has been found by a number of research workers.

One method of determining the amount of solubilizate that will dissolve in a surface-active agent is to prepare a series of tubes of fixed concentration. Increasing amounts of solubilizate are added to the tubes which are then shaken to

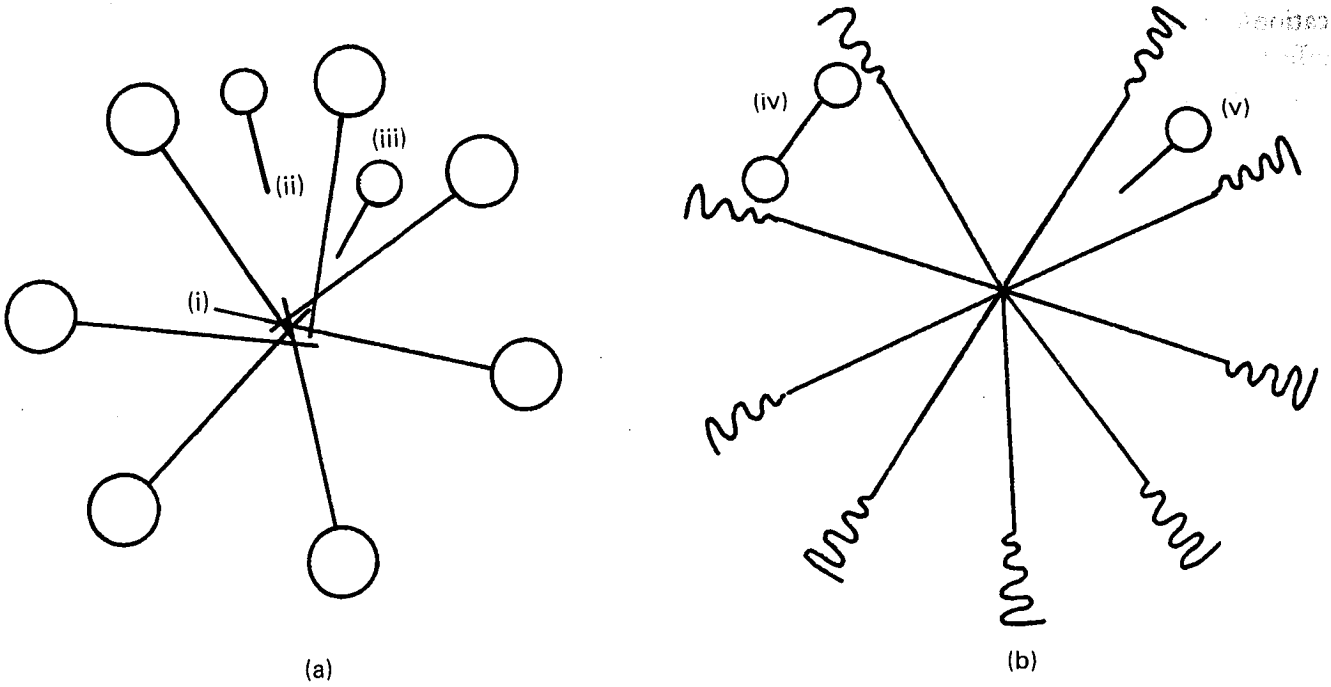


Fig. 6.12 Solubilization in micelles of (a) ionic and (b) non-ionic polyethoxylated surface active agents. See text for details

equilibrate. The maximum concentration of solubilizate forming a clear solution can then be determined visually or from turbidity measurements on the solutions.

Solubility data are expressed as solubility curves or, preferably, as ternary phase diagrams, the latter completely describing the effect of varying the composition of any of the three components of the system. The use of ternary diagrams is described briefly in Chapter 14. For a detailed explanation of the use of such diagrams and of the phenomenon of solubilization the reader is referred to the review by Elworthy *et al.* (1968).

Applications of solubilization

The principle of solubilization is used in the formulation of a large number of drugs. This is discussed in Chapter 14.

Whilst solubilization is an excellent means of producing an aqueous solution of a water-insoluble drug, it should be realized that it may well have effects on the drug's activity and absorption characteristics. As a generalization it may be said that low concentrations of surface-active agents increase absorption, possibly due to enhanced contact of the drug with the absorbing membrane, whilst concentrations above the CMC either produce no additional effect or cause decreased absorption. In the latter case the drug may be held within the micelles so that the concentration available for absorption is reduced. For a survey of this rather complex topic the review by Elworthy *et al.* (1968) should be consulted.

Solubilization and drug stability

Solubilization has been shown to have a modifying effect on the rate of hydrolysis of drugs. Non-polar compounds solubilized deep in the hydrocarbon core of a micelle are likely to be better protected against attack by hydrolysing species than more polar compounds located closer to be micellar surface. Thus, Sheth and Parrott (1967) found that the alkaline hydrolysis of benzocaine and homatropine in the presence of several non-ionic surfactants was retarded. The less polar benzocaine showed a greater increase in stability, compared to homatropine, because of its deeper penetration into the micelle.

An important factor in considering the breakdown of a drug located close to the micellar surface is the ionic nature of the surface-active agent. For base-catalysed hydrolysis anionic micelles should give an enhanced protection due to repulsion of the attacking OH^- group. For

cationic micelles there should be the converse effect. Whilst this pattern has been found, enhanced protection by cationic micelles also occurs, suggesting that in these cases the positively charged polar head groups hold the OH^- groups and thus block their penetration into the micelle.

Protection from oxidative degradation has also been found with solubilized systems.

As indicated earlier drugs may be surface active. Such drugs form micelles and this self-association has been found to increase the drug's stability. Thus micellar solutions of penicillin G have been reported to be 2.5 times as stable as monomeric solutions under conditions of constant pH and ionic strength.

Detergency

Detergency is a complex process whereby surfactants are used for the removal of foreign matter from solid surfaces, be it removal of dirt from clothes or cleansing of body surfaces. The process includes many of the actions characteristic of specific surfactants. Thus the surfactant must have good wetting characteristics so that the detergent can come into intimate contact with the surface to be cleaned. The detergent must have the ability to remove the dirt into the bulk of the liquid; the dirt/water and solid/water interfacial tensions are lowered and thus the work of adhesion between the dirt and solid is reduced, so that the dirt particle may be easily detached. Once removed, the surfactant can be adsorbed at the particle surface creating charge and hydration barriers which prevent deposition. If the dirt is oily it may be emulsified or solubilized.

COARSE DISPERSE SYSTEMS SUSPENSIONS

A pharmaceutical suspension is a coarse dispersion in which insoluble particles, generally greater than 1 μm in diameter, are dispersed in a liquid medium, usually aqueous.

An aqueous suspension is a useful formulation system for administering an insoluble or poorly soluble drug. The large surface area of dispersed drug ensures a high availability for dissolution and hence absorption. Aqueous suspensions may also be used for parenteral and ophthalmic use and provide a suitable form for the applications of dermatological materials to the skin. Suspensions are used similarly in veterinary practice and a closely allied field is that of pest control. Pesticides are frequently presented as suspensions for use as fungicides, insecticides, ascaricides and herbicides.

An acceptable suspension possesses certain desirable qualities among which are the following: the suspended material should not settle too rapidly; the particles which do settle to the bottom of the container must not form a hard mass but should be readily dispersed into a uniform mixture when the container is shaken; and the suspension must not be too viscous to pour freely from the orifice of the bottle or to flow through a syringe needle.

Physical stability of a pharmaceutical suspension may be defined as the condition in which the particles do not aggregate and in which they remain uniformly distributed throughout the dispersion. Since this ideal situation is seldom realized it is appropriate to add that if the particles do settle they should be easily resuspended by a moderate amount of agitation.

The major difference between a pharmaceutical suspension and a colloidal dispersion is one of size of dispersed particles, with the relatively large particles of a suspension liable to sedimentation due to gravitational forces. Apart from this, suspensions show most of the properties of colloidal systems. The reader is referred to Chapter 15 for a detailed account of the formulation of suspensions.

The controlled flocculation approach to suspension formulation

A pharmaceutical suspension which would be thought of as a stable dispersion if considered in terms of the DLVO theory of colloid stability will be deflocculated (the individual solid particles will remain discrete) but will sediment due to the size of the particles. The electrical repulsive forces between the particles will enable them to slip past one another to form a close packed arrangement

at the bottom of the container with the small particles filling the voids between the larger ones. The supernatant liquid may remain cloudy after sedimentation due to the presence of colloidal particles which will remain dispersed. Those particles lowermost in the sediment are gradually pressed together by the weight of the ones above. The repulsive barrier is thus overcome, allowing the particles to pass into close contact with each other. Physical bonding leading to 'cake' or 'clay' formation may then occur due to the formation of bridges between the particles resulting from crystal growth and hydration effects, forces greater than agitation usually being required to disperse the sediment.

Coagulation in the primary minimum, resulting from a reduction in the zeta potential to a point where attractive forces predominate, produces coarse compact masses with a 'curdled' appearance, which may not be readily dispersed.

On the other hand particles flocculated in the secondary minimum form a loosely bonded structure, and, although sedimentation is fairly rapid, a loosely packed high volume sediment is obtained in which the flocs retain their structure and the particles are easily resuspended. The supernatant liquid is clear as the colloidal particles are trapped within the flocs and sediment with them. Thus secondary minimum flocculation is a desirable state for a pharmaceutical suspension. Unfortunately much of the work reported on suspensions in the literature describes aggregation of particles as flocculation and it is not always possible to decide whether it is coagulation or secondary minimum flocculation that has actually occurred.

Particles greater than 1 μm radius should, unless highly charged, show a sufficiently deep secondary minimum for flocculation to occur as the attractive force between particles, V_A, depends on particles size. Other contributing factors to secondary minimum flocculation are shape (asymmetric particles, especially those that are elongated, being more satisfactory than spherical ones) and concentration. The rate of flocculation depends on the number of particles present, so that the greater the number of particles the more collisions there will be and flocculation is more likely to occur. However, it may be necessary, as with highly charged particles, to control the depth of the secondary minimum to induce a satisfactory flocculation state. This can be achieved by addition of electrolytes or ionic surface-active agents which reduce the zeta potential and hence V_R, resulting in the displacement of the whole of the DLVO plot to give a satisfactory secondary minimum as indicated in Fig. 6.4. It will be noted that with a secondary minimum produced in this manner, the distance between the particles is decreased. Hence a more satisfactory compact floc may be produced the particles of which are still easily dispersed. The production of a satisfactory secondary minimum leading to floc formation in this manner is termed *controlled flocculation*.

A convenient parameter for assessing a suspension is the sedimentation volume ratio, F, which is defined as the ratio of the ultimate settled volume V_u to the original volume V_o. F may be expressed as a percentage:

$$F = V_u/V_o \qquad (6.29)$$

The ratio F gives a measure of the aggregated-deflocculated state of a suspension and may usefully be plotted, together with the measured zeta potential, against concentration of additive, enabling an assessment of the state of the dispersion to be made in terms of the DLVO theory. The appearance of the supernatant liquid should be noted and the redispersibility of the suspensions evaluated. For further discussion the reader is referred to the research papers of Kayes (1977a, b) and Rawlins and Kayes (1983).

It should be pointed out that in using the controlled flocculation approach to suspension formulation it is important to work at a constant, or narrow, pH range as the magnitude of the charge on the drug particle can vary greatly with pH (Kayes, 1977b).

Other additives such as flavouring agents may also affect particle charge.

The effect of adsorbed polymer layers on the physical stability of suspensions

As described earlier in this chapter, colloidal particles may be stabilized against coagulation in the absence of a charge on the particles by the use of non-ionic polymeric material, the concept of steric stabilization or protective colloid action.

This concept may be applied to pharmaceutical suspensions where naturally occurring gums such as tragacanth and synthetic materials like non-ionic surfactants and cellulose polymers may be used to produce satisfactory suspensions. These materials may increase the viscosity of the aqueous vehicle and thus slow the rate of sedimentation of the particles but they will also form adsorbed layers around the particles so that the approach of their surfaces and aggregation to the coagulated state is hindered.

Attractive forces exist, of course, between the particles but the tendency now is to look upon attraction as between the polymer layers themselves rather than a modified attraction between uncoated particles (Evans and Napper, 1973). As the two adsorbed layers interpenetrate, however, a repulsion arises — as explained previously, this is enthalpic in origin due to release of water of solvation from the polymer chains with entropy effects due to movement restriction — with the result that, in general, the particles will not approach one another closer than twice the thickness of the adsorbed layer.

However, as indicated above in the discussion on controlled flocculation, from a pharmaceutical point of view an easily dispersed aggregated system is desirable. To produce this state, a balance between attractive and repulsive forces is required. This is not achieved by all polymeric materials, as the equivalent of deflocculated and caked, and coagulated, systems may be produced. The balance of forces appears to depend both on the thickness and the concentration of the polymer in the adsorbed layer. These parameters determine the Hamaker constant and hence the attractive force which must be large enough to cause aggregation of the particles comparable to flocculation. The steric repulsive force, which depends on the concentration and degree of solvation of the polymer chains, must be of sufficient magnitude to prevent close approach of the uncoated particles, but low enough so that the attractive force is dominant leading to aggregation at about twice the adsorbed layer thickness. Thus it has been found that adsorbed layers of certain members of the range of surfactants which are polyoxyethylene–polyoxypropylene block copolymers will produce satisfactory flocculated systems, whilst examples of a nonyl phenyl ethoxylate range will not. With both types of surfactant the molecular moieties producing steric repulsion are hydrated ethylene oxide chains, but the concentration of these in the adsorbed layers varies giving the results indicated above (Rawlins and Kayes, 1980).

Stability of non-aqueous dispersions

A number of non-aqueous dispersions are used in pharmacy. These include oily suspensions such as propyliodine oily injection and phenoxymethylpenicillin mixture, and suspensions of solids in aerosol propellants (these are largely halogenated hydrocarbons such as dichlorodifluoromethane).

As regards the stability of this type of preparation a question that has to be asked is, do the same mechanisms apply as for aqueous systems? Although relatively little work has been carried out in this area, in answering this question it can be said that it is now generally accepted that in rigorously dried material of low polarity (the dielectric constant for water is 80.4 and olive oil 3.1 at 20 °C) the stabilization of dispersions by surface charge mechanisms only plays a minor role, if any, compared to contributions by steric stabilization. The steric stabilizing mechanism is entropic in origin as described earlier in this chapter. However, the stabilizing agents may be different to those used for aqueous systems. Fatty acids and derivatives and polymers based on methacrylates have been used for colloidal dispersions (Vincent, 1973).

With pharmaceutical aerosols there is evidence of steric stabilization of particles dispersed in halogenated hydrocarbons by surface-active agents of low HLB number (see later in this chapter), such as sorbitan trioleate.

Wetting agents

One of the problems encountered in dispersing solid materials in water is that the powder may not be readily wetted (see Chapter 4). This may be due to entrapped air or to the fact that the solid surface is hydrophobic. The wettability of a powder may be described in terms of the contact angle, θ, which the powder makes with the

surface of the liquid. This is shown by Eqn 4.14

$$\gamma_{S/V} = \gamma_{S/L} + \gamma_{L/V} \cos \theta$$

where $\gamma_{S/V}$, $\gamma_{S/L}$ and $\gamma_{L/V}$ are the respective interfacial tensions.

Equation 4.14 may be rearranged to give

$$\cos \theta = \frac{\gamma_{S/V} - \gamma_{S/L}}{\gamma_{L/V}} \qquad (6.30)$$

For a liquid to wet a powder the contact angle must approach zero, or $\cos \theta \rightarrow 1$. In most cases where water is involved this may only be achieved by reducing the magnitude of $\gamma_{L/V}$ and $\gamma_{S/L}$ by use of a wetting agent. Wetting agent are surfactants that are adsorbed at the liquid/vapour and solid/liquid interfaces thus reducing the relevant interfacial tension.

It must be noted that addition of such a surfactant will, as it is adsorbed at the particle surface, also affect the charge characteristics of the solid particle as described under controlled flocculation.

Rheological properties of suspensions

These properties are discussed in more detail in Chapter 2. Flocculated suspensions tend to exhibit plastic or pseudoplastic flow, depending on concentration, while concentrated deflocculated dispersions tend to be dilatant. This means that the apparent viscosity of flocculated suspensions is relatively high when the applied shearing stress is low but it decreases as the applied stress increases and the attractive forces producing the flocculation are overcome. Conversely the apparent viscosity of a concentrated deflocculated suspension is low at low shearing stress but increases as the applied stress increases. This is due to the electrical repulsion which occurs when the charged particles are forced close together — see the DLVO plot of potential energy of interaction between particles (Fig. 6.3) — causing the particles to rebound leaving voids into which the liquid flows, leaving other parts of the dispersion dry.

In addition to the rheological problems associated with particle charge effects the sedimentation behaviour is influenced by the rheological properties of the liquid continuous phase and for this, and other problems encountered with the formulation of suspensions, the reader is referred to the relevant sections of Chapters 2 and 15, respectively.

EMULSIONS

An emulsion is a system consisting of two immiscible liquid phases, one of which, in fine droplets, is dispersed throughout the other. Such an emulsion is thermodynamically unstable and it is usually necessary to add a third component, the emulsifying agent.

The phase which is present as fine droplets is called the disperse phase and the phase in which the droplets are suspended the continuous phase. Most emulsions will have droplets with diameters of 0.1–100 μm; smaller globules exhibit colloidal behaviour and the stability of a hydrophobic colloidal dispersion.

Pharmaceutical emulsions usually consist of water and an oil. Two types of emulsion can exist, oil in water (o/w) and water in oil (w/o) depending upon whether the continuous phase is aqueous or oily. More complicated emulsion systems may exist; for example, an oil droplet enclosing a water droplet may be suspended in water to form a water in oil in water emulsion (w/o/w). Such as system or its o/w/o counterpart — termed *multiple emulsions* — may occur particularly in the neighbourhood of the emulsion inversion point. These multiple emulsions are of interest as delayed action drug delivery systems. Traditionally emulsions have been used to render oily substances such as castor oil and liquid paraffin in a more palatable form. It is possible to formulate together oil-soluble and water-soluble medicaments and drugs may be more easily absorbed owing to the finely divided condition of emulsified substances. Thus there is enhanced absorption of griseofulvin when presented suspended in oil in an o/w emulsion (Carrigan and Bates, 1973). Details of the formulation of emulsions is given in Chapter 16.

A large number of bases used for topical preparations are emulsions, water miscible being o/w type and greasy bases w/o. The administration of oils and fats by intravenous infusion, as part of a total parenteral nutrition programme, has been made possible by the use of suitable non-toxic emulsifying agents like lecithin. Here, the control

of particle size of emulsion droplets is of paramount importance in the prevention of formation of emboli.

Microemulsions

As shown previously oils can be brought into solution by solubilization. It is difficult to make a sharp distinction between emulsification and solubilization since there is a gradual transition from one form into the other as the relative proportion of oil to surface-active agent is altered, a high proportion of surfactant being required for solubilization, lower for emulsification.

At the transition stage swollen micellar systems or *microemulsions* are likely to occur. An apparently isotropic system is obtained containing a high percentage of both oil and water and a high concentration of surfactant. These are essentially swollen micellar systems but it is difficult to assess the difference between a swollen micelle and a small emulsion droplet.

Theory of emulsion stabilization

Interfacial free energy and emulsification

When two immiscible liquids, e.g. liquid paraffin and water, are shaken together a temporary emulsion will be formed. The subdivision of one of the phases into small globules results in a large increase in surface area and thus interfacial free energy of the system. The system is thus thermodynamically unstable which results, in the first place, in the dispersed phase being in the form of spherical droplets (the shape of minimum surface area for a given volume) and secondly in coalescence of these droplets, causing phase separation, the state of minimum surface free energy.

The adsorption of a surface-active agent at the globule interface will lower the o/w interfacial tension, the process of emulsification will be made easier and the stability may be enhanced. However, if a surface-active agent such as sodium dodecyl sulphate is used, the emulsion, on standing for a short while, will still separate out into its constituent phases. On the other hand, substances like acacia, which are only slightly surface active, produce stable emulsions. Acacia forms a strong viscous interfacial film around the globules and it is considered that the characteristics of the interfacial film, are most important in considering the stability of emulsions.

Whether or not a surface-active agent will stabilize an emulsion will depend on the type of film formed at the o/w interface (for a discussion on monolayer film characteristics the reader should refer to a publication such as that by Adam, 1970). Sodium dodecyl sulphate forms what is termed a gaseous film at the o/w interface. One of the properties of this type of film is that the molecules forming it are separate and free to move in the interface. As one film-covered droplet approaches another the charged head groups of the sodium dodecyl sulphate repel each other. If the charged groups were fixed at the interface this repulsion would confer stability on the emulsion droplets, but as they are not, surfactant molecules move away from corresponding areas of the droplets, allowing them to coalesce. On the other hand, a surface-active agent which forms a more condensed type film, such as sodium oleate, where the molecules are not free to move in the interface, produces a stable emulsion.

Interfacial complexes

Applying knowledge gained by studying monolayers at the air/water interface Schulman and Cockbain (1940) found that a mixture of an oil-soluble alcohol such as cholesterol and a surface-active agent such as sodium cetyl (hexadecyl) sulphate was able to form a stable complex condensed film at the oil/water interface. This film was of high viscosity, flexible, permitting distortion of the droplets, resisted rupture and gave an interfacial tension lower than that produced by either component alone, of extremely low value. The emulsion produced was stable, the charge arising from the sodium cetyl sulphate contributing to the stability as described for lyophobic colloidal dispersions.

For complex formation at the interface the correct 'shape' of molecule is necessary, thus Schulman and Cockbain found that sodium cetyl sulphate stabilized an emulsion of liquid paraffin when elaidyl alcohol (the *trans* isomer) was the oil-soluble component but not when the *cis* isomer, oleyl alcohol, was used.

In practice, applying the findings of Schulman and Cockbain, the oil-soluble and water-soluble components are dissolved in the appropriate phases; on mixing the two phases the complex is formed at the interface. Alternatively, an emulsifying wax may be used which consists of both components blended together. The wax is dispersed in the oil phase and the aqueous phase added at the same temperature. Examples of such mixtures are given in Table 6.4.

Table 6.4 Emulsifying waxes

Product	*Oil-soluble component*	*Water-soluble component*
Emulsifying wax (anionic)	Cetostearyl alcohol	Sodium lauryl (dodecyl) sulphate
Cetrimide emulsifying wax (cationic)	Cetostearyl alcohol	Cetrimide (hexadecyl trimethyl ammonium bromide)
Cetomacrogol emulsifying wax (non-ionic)	Cetostearyl alcohol	Cetomacrogol (polyoxyethylene monohexadecyl ether)

This principle is also applied with the non-ionic emulsifying agents which are sorbitan esters, for example sorbitan mono-oleate and polyoxyethylene sorbitan esters (e.g. polysorbate 80), mixtures of the two types giving the best results. These emulsifying agents are not charged and there is no electrical repulsive force contributing to stability. It is likely, however, that these substances, and the cetomacrogol emulsifying wax as mentioned above, sterically stabilize the emulsions as mentioned in the next section.

Emulsion stabilization by non-ionic surfactants

Non-ionic surfactants are widely used in the production of stable emulsions. They are generally less toxic than ionic surfactants and are less sensitive to electrolytes and pH variation. Examples include sorbitan esters, polysorbates and straight chain compounds such as the polyoxyethylene glycol monoethers of *n*-alkanols of which cetomacrogol is an example.

These surfactants form interfacial films at the o/w interface in the same way as discussed in the previous section, but, as the molecules are not charged, there is no electrostatic repulsive contribution to stability. However, the polar groups of the surfactant molecules consist largely of hydrated ethylene oxide chains and these bring about a steric repulsion in exactly the same way as discussed under suspensions.

For a comprehensive review of this subject readers should consult the review by Florence and Rogers (1971).

Hydrophilic colloids as emulsion stabilizers

A number of hydrophilic colloids are used as emulsifying agents in pharmacy. These include proteins (gelatin, casein) and polysaccharides (acacia, cellulose derivatives and alginates).

These materials, which generally exhibit little surface activity, adsorb at the oil/water interface and form multilayers. Thus Shotton and White (1963) demonstrated films of acacia of thickness of the order of 0.25 μm. Such multilayers have viscoelastic properties, resist rupture and presumably form mechanical barriers to coalescence. However, some of these substance have chemical groups which ionize, e.g. acacia consists of salts of arabic acid, proteins contain both amino and carboxylic acid groupings, thus providing electrostatic repulsion as an additional barrier to coalescence.

Most cellulose derivatives are not charged. There is evidence, however, from studies on solid suspensions, that these substances sterically stabilize and it would appear probable that there will be a similar effect with emulsions (Law and Kayes, 1983).

Solid particles in emulsion stabilization

Emulsions may be stabilized by finely divided solid particles if they are preferentially wetted by one phase and possess sufficient adhesion for one another so that they form a film around the dispersed droplets.

Solid particles will remain at the interface as long as a stable contact angle, θ, is formed by the liquid/liquid interface and the solid surface. The particles must also be of sufficiently low mass for gravitational forces not to affect the equilibrium.

Then Eqn 4.14 for two liquids A and B and a solid S becomes

$$\gamma_{B/S} = \gamma_{A/S} + \gamma_{A/B} \cos \theta$$

If a contact angle is not formed then the particle remains entirely in one of the liquid phases, and if $\gamma_{B/S} > \gamma_{A/S} + \gamma_{A/B}$ the particle will be totally immersed in liquid A and if $\gamma_{A/S} > \gamma_{B/S} + \gamma_{A/B}$ the particle will be totally immersed in liquid B. The liquid which preferentially wets the solid, that is the one whose angle of contact measured through that liquid is less than 90°, will form the continuous phase. Under these circumstances a curved surface is best for the particles to form a close packed layer at the interface with the major part of the solid in the continuous phase and the liquid least effective in wetting the solid forming the disperse phase.

Aluminium and magnesium hydroxides and clays such as bentonite are preferentially wetted by water and thus stabilize o/w emulsions, e.g. liquid paraffin and magnesium hydroxide emulsion.

Carbon black and talc are more readily wetted by oils and stabilize w/o emulsions.

For details of methods of preparation of emulsions and formulation aspects the reader is referred to Carter (1975) and Chapter 16 of this publication.

Emulsion type

When an oil, water and an emulsifying agent are shaken together, what decides whether an o/w or w/o emulsion will be produced? A number of simultaneous processes have to be considered, for example droplet formation, aggregation and coalescence of droplets, and interfacial film formation. On shaking together oil and water both phases initially form droplets. The phase that persists in droplet form for a longer period of time should become the disperse phase and it should be surrounded by the continuous phase formed from the more rapidly coalescing droplets. The phase volumes and interfacial tensions will determine the relative number of droplets produced and hence the probability of collision, i.e. the greater the number of droplets the higher the chance of collision, so that the phase present in greater amount should finally become the continuous phase. However, emulsions containing well over 50% of disperse phase are common.

A more important consideration is the interfacial film produced by the adsorption of emulsifier at the o/w interface. Such films significantly alter the rates of coalescence by acting as physical and chemical barriers to coalescence. As indicated in the previous section the barrier at the surface of an oil droplet may arise because of electrically charged groups producing repulsion between approaching droplets or because of the steric repulsion, enthalpic in origin, from hydrated polymer chains. The greater the number of charged molecules present, or the greater the number of hydrated polymer chains, at the interface the greater will be the tendency to reduce oil droplet coalescence. On the other hand the interfacial barrier for approaching water droplets arises primarily because of the non-polar or hydrocarbon portion of the interfacial film. The longer the hydrocarbon chain length and the greater the number of molecules present per unit area of film, the greater is the tendency for water droplets to be prevented from coalescing. Thus it may be said generally that it is the dominance of the polar or non-polar characteristics of the emulsifying agent which plays a major contribution to the type of emulsion produced. For a more complete discussion of this concept the reader is referred to the text by Davies and Rideal (1963).

It would appear then, that the type of emulsion formed, depending as it does on the polar/non-polar characteristics of the emulsifying agent, is a function of the relative solubility of the emulsifying agent, the phase in which it is more soluble being the continuous phase. This is a statement of what is termed the Bancroft rule, an empirical observation made in 1913.

The foregoing helps to explain why charged surface-active agents such as sodium and potassium oleates which are highly ionized and possess strong polar groups favour o/w emulsions, whereas calcium and magnesium soaps which are little dissociated tend to produce w/o emulsions. Similarly, non-ionic sorbitan esters favour w/o emulsions whilst o/w emulsions are produced by the more hydrophilic polyoxyethylene sorbitan esters.

By reason of the stabilizing mechanism involved, polar groups are far better barriers to coalescence than their non-polar counterparts. It is thus possible to see why o/w emulsions can be

made with greater than 50% disperse phase and why w/o emulsions are limited in this respect and will easily invert (change type) if the amount of water present is significant.

Pharmaceutical preferences for o/w or w/o are discussed in Chapter 16.

Hydrophile–lipophile balance (HLB)

The fact that a more hydrophilic interfacial barrier favours o/w emulsions whilst a more non-polar barrier favours w/o emulsions is made use of in the hydrophile–lipophile balance (HLB) system for assessing surfactants and emulsifying agents, which was introduced by Griffin in 1949. Here an HLB number is assigned to an emulsifying agent which is characteristic of its relative polarity. Although originally conceived for non-ionic emulsifying agents with polyoxyethylene hydrophilic groups (where the precentage weight of the hydrophilic group is divided by 5 to give the HLB number), it has since been applied with varying success to other surfactant groups, both ionic and non-ionic.

By means of this number system an HLB range of optimum efficiency for each class of surfactant is established as seen in Fig. 6.13. This approach is empirical but it does allow comparison between different chemical types of emulsifying agent. Comparison of properties like solubility, interfacial tension and CMC have also been used to compare a surfactant with one of known HLB value.

Typical HLB values for some pharmaceutical surfactants are given in Table 16.2.

In addition it has been suggested that certain emulsifying agents of a given HLB value appear to work best with a particular oil phase and this has given rise to the concept of a required HLB value for any oil or combination of oils, this value may be ascertained by observing emulsion stability.

For reasons mentioned earlier, when discussing interfacial films, mixtures of surface active agents give more stable emulsions than when used singly. The HLB of a mixture of surfactants, consisting of fraction x of A and $(1 - x)$ of B, is assumed to be an algebraic mean of the two HLB numbers.

$$HLB_{Mixture} = x\ HLB_A + (1 - x)\ HLB_B$$

It has been found that, at the optimum HLB for a particular emulsion, the mean particle size of the emulsion is at a minimum and this factor contributes to the stability of the emulsion system. The use of HLB values in the formulation of emulsions is discussed in Chapter 16.

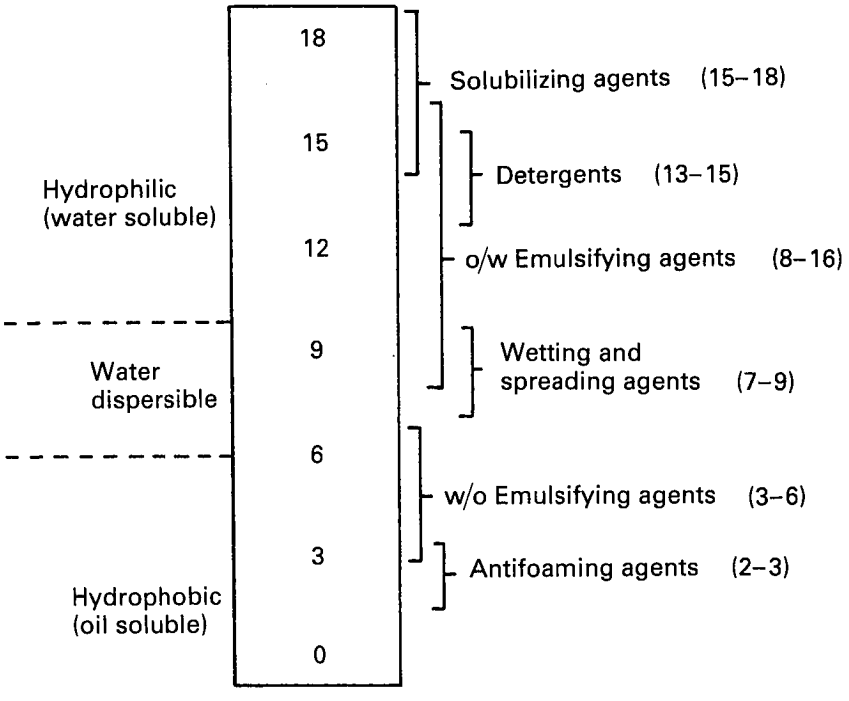


Fig. 6.13 HLB scale showing classification of surfactant function

Phase viscosity

The emulsification process and the type of emulsion formed are influenced to some extent by the viscosity of the two phases. Viscosity can be expected to affect interfacial film formation as the migration of molecules of emulsifying agent to the oil/water interface is diffusion controlled. Droplet movement prior to coalescence is also affected by the viscosity of the medium in which the droplets are dispersed.

Determination of emulsion type

Several tests are available to distinguish between o/w and w/o emulsions (see Chapter 16).

Stability of emulsions

A stable emulsion may be defined as a system in which the globules retain their initial character and remain uniformly distributed throughout the continuous phase. The function of the emulsifying agent is to form an interfacial film around the dispersed droplets; the physical nature of this barrier controls whether or not the droplets will coalesce as they approach one another. If the film is electrically charged then repulsive forces will contribute to stability.

Separation of an emulsion into its constituent phases is termed *cracking* or *breaking*.

It follows that any agent that will destroy the interfacial film will crack the emulsion. Some of the factors that cause an emulsion to crack are

1 the addition of a chemical that is incompatible with the emulsifying agent, thus destroying its emulsifying ability. Examples include surface-active agents of opposite ionic charge, e.g. the addition of cetrimide (cationic) to an emulsion stabilized with sodium oleate (anionic); addition of large ions of opposite charge, e.g. neomycin sulphate (cationic) to aqueous cream (anionic); addition of electrolytes such as calcium and magnesium salts to emulsion stabilized with anionic surface-active agents;
2 bacterial growth — protein materials and non-ionic surface-active agents are excellent media for bacterial growth;
3 temperature change — protein emulsifying agents may be denatured and the solubility characteristics of non-ionic emulsifying agents change with a rise in temperature, heating above 70 °C destroys most emulsions. Freezing will also crack an emulsion; this may be due to the ice formed disrupting the interfacial film around the droplets.

Other ways in which an emulsion may show instability are as follows.

Flocculation

Even though a satisfactory interfacial film is present around the oil droplets, secondary minimum flocculation, as described earlier in this chapter under the discussion on the DLVO theory of colloid stability, is likely to occur with most pharmaceutical emulsions. The globules do not coalesce and may be redispersed by shaking. However, due to the closeness of approach of droplets in the floccule, if any weaknesses in the interfacial films occurs then coalescence may follow. Flocculation should not be confused with creaming (see below). The former is due to the interaction of attractive and repulsive forces and the latter due to density differences in the two phases, both may occur.

Phase inversion

As indicated under the section on emulsion type, phase volume ratio is a contributory factor to the type of emulsion formed. Although it was stated there that stable emulsions containing more than 50% of disperse phase are common, attempts to incorporate excessive amounts of disperse phase may cause cracking of the emulsion or phase inversion (conversion of an o/w emulsion to w/o or vice versa). It can be shown that uniform spheres arranged in the closest packing will occupy 74.02% of the total volume irrespective of their size. Thus Ostwald suggested that an emulsion which resembles such an arrangement of spheres would have a maximum disperse phase concentration of the same order. Although it is possible to obtain more concentrated emulsions than this, because of the non-uniformity of size of the globules and the possibility of deformation of shape of the globules, there is a tendency for

emulsions containing more than about 70% disperse phase to crack or invert.

Further, any additive that alters the hydrophile–lipophile balance of an emulsifying agent may alter the emulsion type, thus addition of a magnesium salt to an emulsion stabilized with sodium oleate will cause the emulsion to crack or invert.

The addition of an electrolyte to anionic and cationic surfactants may suppress their ionization due to the common ion effect and thus a w/o emulsion may result even though normally an o/w emulsion would be produced, e.g. White Liniment BP is formed from turpentine oil, ammonium oleate, ammonium chloride and water. With ammonium oleate as emulsifying agent an o/w emulsion would be expected, but the suppression of ionization of the ammonium oleate by the ammonium chloride (the common ion effect) and a relatively large volume of turpentine oil, produce a w/o emulsion.

Emulsions stabilized with non-ionic emulsifying agents such as the polysorbates may invert on heating. This is due to the breaking of the H-bonds responsible for the hydrophilic characteristics of the polysorbate; its HLB value is thus altered and the emulsion inverts.

Creaming

Many emulsions cream on standing. The disperse phase, according to its density relative to that of the continuous phase, rises to the top or sinks to the bottom of the emulsion forming a layer of more concentrated emulsion. A common example is milk, an o/w emulsion, with cream rising to the top of the emulsion.

As mentioned earlier flocculation may occur as well as creaming but not necessarily so. Droplets of the creamed layer do not coalesce as may be found by gentle shaking which redistributes the droplets throughout the continuous phase. Although not so serious an instability factor as cracking, creaming is undesirable from a pharmaceutical point of view because a creamed emulsion is inelegant in appearance, provides the possibility of inaccurate dosage, and increases the likelihood of coalescence since the globules are close together in the cream.

Those factors which influence the rate of creaming are similar to those involved in the sedimentation rate of suspension particles and are indicated by Stokes' law (Eqn 6.6) as follows:

$$v = \frac{2a^2g(\sigma - \rho)}{9\eta}$$

here v is the velocity of creaming, a the globule radius, $\sigma - \rho$ the densities of disperse phase and dispersion medium respectively and η the viscosity of the dispersion medium. A consideration of this equation shows that the rate of creaming will be decreased:

1 by reduction in the globule size,
2 a decrease in the density difference between the two phases, and
3 an increase in the viscosity of the continuous phase.

This may be achieved by homogenizing the emulsion to reduce the globule size and increasing the viscosity of the continuous phase η by the use of thickening agents such as tragacanth or methylcellulose. It is seldom possible to satisfactorily adjust the densities of the two phases.

Assessment of emulsion stability

Approximate assessments of the relative stabilities of a series of emulsions may be obtained from estimations of the degree of separation of the disperse phase as a distinct layer, or from the degree of creaming. Whilst separation of the emulsion into two layers, i.e. cracking, indicates gross instability, a stable emulsion may cream, creaming being simply due to density differences and easily reversed by shaking. Some coalescence may, however, take place due to the close proximity of the globules in the cream, similar problems occur with flocculation.

However, instability in an emulsion results from any process which causes a progressive increase in particle size and a broadening of the particle size distribution, so that eventually the dispersed particles become so large that they separate out as free liquid. Accordingly, a more precise method for assessing emulsion stability is to follow the globule size distribution with time. An emulsion approaching the unstable state is characterized by

the appearance of large globules as a result of the coalescence of others. Methods for determining particle size distribution have been reviewed by Sherman (1968).

Phase inversion temperature

One of the methods for predicting emulsion stability is the phase inversion temperature (PIT) technique of Parkinson and Sherman (1972). He has shown that the kinetics of globule coalescence in w/o and o/w emulsions stabilized by non-ionic emulsifying agents are influenced by the HLB values of the emulsifiers, i.e. as indicated earlier there is an optimum HLB value giving greatest stability for a particular emulsion system. Now the solubility of non-ionic surfactants, and hence the HLB, change when the temperature is raised, due to breaking of H-bonds, so that as mentioned previously the emulsion can invert. Sherman found a relationship between the PIT of o/w emulsions stabilized by non-ionic emulsifying agents and the rate of globule coalescence so that it should be possible to evaluate emulsion stability from PIT determinations, as the phase inversion temperature increases so globule coalescence decreases, i.e., the more stable the emulsion.

FOAMS

A foam is a coarse dispersion of a gas in a liquid which is present as thin films or lamellae of colloidal dimensions between the gas bubbles.

Foams find application in pharmacy as aqueous and non-aqueous spray preparations for topical, rectal and vaginal medication and for burn dressings. Equally important, however, is the destruction of foams and the use of antifoaming agents. These are not only of importance in manufacturing processes, preventing foam in for example liquid preparations, but foam inhibitors like the silicones are used in the treatment of flatulence, for the elimination of gas, air or foam from the gastrointestinal tract prior to radiography and for the relief of abdominal distension and dyspepsia.

Due to their high interfacial area (and surface-free energy) all foams are unstable in the thermodynamic sense. Their stability depends on two major factors — the tendency for the liquid films to drain and become thinner and their tendency to rupture due to random disturbances such as vibration, heat and diffusion of gas from small bubbles to large bubbles. Gas diffuses from the small bubbles to the large because the pressure in the former is greater, this is a phenomenon of curved interfaces and is described by the Kelvin equation (see Eqn 4.1 and Shaw, 1980 for a fuller description). The holes thus gradually merge to become larger and the foam gradually collapses.

Pure liquids do not foam. Transient or unstable foams are obtained with solutes such as short chain acids and alcohols which are mildly surface active. However, persistent foams are formed by solutions of surfactants. The film in such foams consists of two monolayers of adsorbed surface-active molecules separated by an aqueous core. The surfactants stabilize the film by means of electrical double layer repulsion or steric stabilization as described for colloidal dispersions.

Foams are often troublesome and knowledge of the action of substances that cause their destruction is useful. There are two types of antifoaming agent:

1 *foam breakers* such as ether and *n*-octanol. These substances are highly surface active and are thought to act by lowering the surface tension over small regions of the liquid film. These regions are rapidly pulled out by surrounding regions of higher tension, small areas of film are therefore thinned out and left without the properties to resist rupture.
2 *foam inhibitors*, such as polyamides and silicones. It is thought that these are adsorbed at the air/water interface in preference to the foaming agent, but they do not have the requisite ability to form a stable foam. They have a low interfacial tension in the pure state and may be effective by virtue of rapid adsorption.

AEROSOLS

Aerosols are colloidal dispersions of liquids or solids in gases. In general mists and fogs possess liquid disperse phases whilst smoke is a dispersion of solid particles in gases. However, no sharp

distinction can be made between the two kinds because liquid is often associated with the solid particles. A *mist* consists of fine droplets of liquid which may or may not contain dissolved or suspended material. If the concentration of droplets becomes high it may be called a *fog*.

While all the disperse systems mentioned above are less stable than colloids which have a liquid as dispersion medium they have many properties in common with the latter and can be investigated in the same way. Particle size is usually within the colloidal range but if larger than 1 μm the life of an aerosol is short because the particles settle out too quickly.

Preparation of aerosols

In common with other colloidal dispersions aerosols may be prepared by either dispersion or condensation methods. The latter involve the initial production of supersaturated vapour of the material that is to be dispersed. This may be achieved by supercooling the vapour. The supersaturation eventually leads to the formation of nuclei, which grow into particles of colloidal dimensions. The preparation of aerosols by dispersion methods is of greater interest in pharmacy and may be achieved by the use of pressurized containers with, for example, liquefied gases such as halogenated hydrocarbons as the propellants. If a solution or suspension of active ingredients is contained in the liquid propellant or in a mixture of this liquid and an additional solvent, then when the valve on the container is opened the vapour pressure of the propellant forces the mixture out of the container. The large expansion of the propellant at room temperature and atmospheric pressure produces a dispersion of the active ingredients in air. Although the particles in such dispersions are often larger than those in colloidal systems, the term aerosols is still generally applied to them.

Applications of aerosols in pharmacy

The use of aerosols as a dosage form is particularly important in the administration of drugs via the respiratory system. In addition to local effects, systemic effects may be obtained if the drug is absorbed into the blood stream from the lungs. Topical preparations are also well suited for presentation as aerosols. In the closely allied field of pesticides, insecticide aerosol preparations are widely used.

For a fuller account of the subject of therapeutic aerosols the reader is referred to Chapter 20.

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