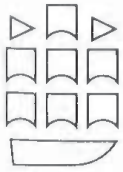
Pharmaceutics: The Science of Dosage Form Design

EDITED BY

Michael E. Aulton BPharm PhD MPS
Reader in Pharmacy, Leicester Polytechnic, Leicester, UK



CHURCHILL LIVINGSTONE
EDINBURGH LONDON MELBOURNE AND NEW YORK 1988

CHURCHILL LIVINGSTONE
Medical Division of Longman Group UK Limited
Distributed in the United States of America by
Churchill Livingstone Inc., 1560 Broadway, New
York, N.Y. 10036, and by associated companies,
branches and representatives throughout the world.

First published 1988

ISBN 0-443-03643-8

British Library Cataloguing in Publication Data
Pharmaceutics: the science of dosage form
design.
1. Pharmaceutics
I. Aulton, Michael E.
615'.19 RS403

Library of Congress Cataloging in Publication Data
Pharmaceutics: the science of dosage form design.
Replaces: Cooper and Gunn's tutorial pharmacy.
6th ed. 1972.
Includes bibliographies and index.
1. Drugs — Design of delivery systems. 2. Drugs
— Dosage forms. 3. Biopharmaceutics.
4. Pharmaceutical technology. 5. Chemistry,
Pharmaceutical. 6. Microbiology, Pharmaceutical.
I. Aulton, Michael E.
[DNLM: 1. Biopharmaceutics. 2. Chemistry,
Pharmaceutical. 3. Dosage Forms. 4. Technology,
Pharmaceutical. 5. Microbiology, Pharmaceutical.
QV 785 P5366]
~~RS420.P48 1987~~ 615.5'8 86–25888

Produced by Longman Group (FE) Ltd
Printed in Hong Kong

Preface

The first edition of *Pharmaceutics* has replaced the 6th edition of *Cooper and Gunn's Tutorial Pharmacy* published by Pitman in 1972. Since then, there has been a change in editorship, a change in the title of the book, a change in some of the authors and a completely redesigned content. But all is not new and disjointed, the editorial link with Leicester School of Pharmacy continues. Sidney Carter recently retired as Deputy Head of Leicester School of Pharmacy and passed on the book to me. He in turn had inherited the book from one of its founders, the late Colin Gunn who was formerly Head of Leicester School of Pharmacy but sadly died on 25 February 1983.

There are a greater number and a wider range of authors in this edition, each an accepted expert in the field on which they have written and, just as important, each has experience and ability in imparting that information to undergraduate pharmacy students.

The philosophy of the subject matter which the book covers has changed because pharmaceutics has changed. Since the last edition of *Tutorial Pharmacy* there have been very marked changes in the concept and content of pharmaceutics. Those changes are reflected in this edition. The era of biopharmaceutics was in its infancy at the time of the previous edition. Since then we have become increasingly concerned with not merely producing elegant and accurate dosage forms but also ensuring that the optimum amount of drug reaches the required place in the body and stays there for the optimum amount of time. Now we are concerned much more with designing dosage forms and with all aspects of drug delivery. This book reflects that concern.

Dr M E Aulton
School of Pharmacy
Leicester Polytechnic

3

J H Richards

Solutions and their properties

The main aim of this chapter and Chapter 5 is to provide information on certain physicochemical principles that relate to the applications and implications of solutions in pharmacy. For the purposes of the present discussion these principles have been classified in a somewhat arbitrary manner. Thus, this chapter deals mainly with the physicochemical properties of solutions that are important with respect to systems and processes described in other parts of this book or in the companion volume, *Dispensing for Pharmaceutical Students* by Carter (1975) (new edition in preparation). Chapter 5 on the other hand is concerned with the principles underlying the formation of solutions and the factors that affect the rate and extent of this dissolution process. Because of limitations of space and the number of principles and properties that need to be considered the contents of each of these chapters should only be regarded as introductions to the various topics. The student is encouraged, therefore, to refer to the bibliography cited at the end of each chapter in order to augment the present contents. The textbook written by Florence and Attwood (1981) is recommended particularly, because of the large number of pharmaceutical examples that are used to aid understanding of physicochemical principles.

DEFINITION OF TERMS

A solution may be defined as a mixture of two or more components that form a single phase, which is homogeneous down to the molecular level. The component that determines the phase of the solution is termed the solvent and usually consti-

tutes the largest proportion of the system. The other components are termed solutes and these are dispersed as molecules or ions throughout the solvent; i.e. they are said to be dissolved in the solvent. The extent to which the dissolution proceeds under a given set of experimental conditions is referred to as the solubility of the solute in the solvent. Thus, the solubility of a substance is the amount of it that passes into solution when an equilibrium is established between the solution and excess, i.e. undissolved, substance. The solution that is obtained under these conditions is said to be saturated. Since the above definitions are general ones they may be applied to all types of solution. However, when the two components forming a solution are either both gases or both liquids then it is more usual to talk in terms of miscibility rather than solubility.

Methods of expressing concentration

Quantity per quantity

Concentrations are often expressed simply as the weight or volume of solute that is contained in a given weight or volume of the solution. The majority of solutions encountered in pharmaceutical practice consist of solids dissolved in liquids. Consequently, concentration is expressed most commonly by the weight of solute contained in a given volume of solution. Although the SI unit is kg m^{-3} the terms that are used in practice are based on more convenient or appropriate weights and volumes. For example, in the case of a solution with a concentration of 1 kg m^{-3} the strength may be denoted by any one of the following concentration terms depending on the circumstances:

1 g l^{-1}, 0.1 g per 100 ml, 1 mg ml^{-1}, 5 mg in 5 ml or 1 μg μl^{-1}.

Percentage

The British and European Pharmacopoeias use the same method as a basis for their percentage expressions of the strengths of solutions. For example, the concentration of a solution of a solid in a liquid would be given by

$$\text{concentration in \% w/v} = \frac{\text{weight of solute}}{\text{volume of solution}} \times 100$$

Per cent v/w, % v/v and % w/w expressions are also referred to in the *General Notices* of the *British Pharmacopoeia* (1980) together with the statement that the latter two expressions are used for solutions of liquids in liquids and solutions of gases in liquids, respectively.

It should be realized that if concentration is expressed in terms of weight of solute in a given volume of solution then changes in volume caused by temperature fluctuations will alter the concentration.

Parts

The Pharmacopoeia also expresses some concentrations in terms of the number of 'parts' of solute dissolved in a stated number of 'parts' of solution. Use of this method to describe the strength of a solution of a solid in a liquid infers that a given number of parts by volume (ml) of solution contain a certain number of parts by weight (g) of solid. In the case of solutions of liquids in liquids parts by volume of solute in parts by volume of solution are intended whereas with solutions of gases in liquids parts by weight of gas in parts by weight of solution are inferred.

Molarity

This is the number of moles of solute contained in 1 dm^3 (or, more commonly in pharmacy, 1 litre) of solution. Thus, solutions of equal molarity contain the same number of solute molecules in a given volume of solution. The unit of molarity is mol l^{-1} (equivalent to 10^3 mol m^{-3} if converted to the SI unit). Although use of the term molar concentration and its symbol M to describe the molarity of a solution has been discouraged since the introduction of SI units the symbol M is still used in the current British and European Pharmacopoeias.

Molality

This is the number of moles of solute divided by the mass of the solvent, i.e. its SI unit is

mol kg^{-1}. Although it is less likely to be encountered in pharmaceutical practice than the other terms it does offer a more precise description of concentration because it is unaffected by temperature.

Mole fraction

This is often used in theoretical considerations and is defined as the number of moles of solute divided by the total number of moles of solute and solvent, i.e.

$$\text{mole fraction of solute } (x_1) = \frac{n_1}{n_1 + n_2}$$

where n_1 and n_2 are the numbers of moles of solute and solvent, respectively.

Milliequivalents and normal solutions

The concentrations of solutes in body fluids and in solutions used as replacements for these fluids are usually expressed in terms of the number of millimoles (1 millimole = one thousandth of a mole) in a litre of solution. In the case of electrolytes, however, these concentrations may still be expressed in terms of milliequivalents per litre. A milliequivalent (mEq) of an ion is, in fact, one thousandth of the gram equivalent of the ion, which is, in turn, the ionic weight expressed in grams divided by the valency of the ion. Alternatively,

$$1 \text{ mEq} = \frac{\text{ionic weight in mg}}{\text{valency}}$$

A knowledge of the concept of chemical equivalents is also required in order to understand the use of 'normality' as a means of expressing the concentration of solutions, because a normal solution, i.e. concentration = 1 N, is one that contains the equivalent weight of the solute, expressed in grams, in 1 litre of solution. It was thought that this term would disappear on the introduction of SI units but it is still encountered in some volumetric assay procedures, e.g. in *British Pharmacopoeias* preceding the 1980 edition and in the current *European Pharmacopoeia*. The student is referred to Beckett and Stenlake (1975) for an explanation of chemical equivalents.

TYPES OF SOLUTION

Solutions may be classified on the basis of the physical states, i.e. gas, solid or liquid, of the solute(s) and solvent. Although a variety of different types can exist, solutions of pharmaceutical interest virtually all possess liquid solvents. In addition, the solutes are predominantly solid substances. Consequently, most of the comments given in this chapter and in Chapter 5 are made with solutions of solids in liquids in mind. However, appropriate comments on other types, e.g. gases in liquids, liquids in liquids and solids in solids are included.

Vapour pressures of solids, liquids and solutions

An understanding of many of the properties of solutions requires an appreciation of the concept of an ideal solution and its use as a reference system, to which the behaviours of real (non-ideal) solutions can be compared. This concept is itself based on a consideration of vapour pressure. The present section is included, therefore, as an introduction to the later discussions on ideal and non-ideal solutions.

The kinetic theory of matter indicates that the thermal motions of molecules of a substance in its gaseous state are more than adequate to overcome the attractive forces that exist between the molecules, so that the molecules undergo a completely random movement within the confines of the container. The situation is reversed, however, when the temperature is lowered sufficiently so that a condensed phase is formed. Thus, the thermal motions of the molecules are now insufficient to overcome completely the intermolecular attractive forces and some degree of order in the relative arrangement of molecules occurs. If the intermolecular forces are so strong that a high degree of order, which is hardly influenced by thermal motions, is brought about then the substance is usually in the solid state.

In the liquid condensed state the relative influences of thermal motion and intermolecular attractive forces are intermediate between those in the gaseous and solid states. Thus, the effects of interactions between the permanent and induced

dipoles, i.e. the so-called van der Waals forces of attraction, lead to some degree of coherence between the molecules of liquids. Consequently, liquids occupy a definite volume, unlike gases, and whilst there is evidence of structure within liquids such structure is much less apparent than in solids.

Although solids and liquids are condensed systems with cohering molecules some of the surface molecules in these systems will occasionally acquire sufficient energy to overcome the attractive forces exerted by adjacent molecules and so escape from the surface to form a vaporous phase. If temperature is maintained constant an equilibrium will be established eventually between the vaporous and condensed phases and the pressure exerted by the vapour at equilibrium is referred to as the vapour pressure of the substance.

All condensed systems have the inherent ability to give rise to a vapour pressure. However, the vapour pressures exerted by solids are usually much lower than those exerted by liquids, because the intermolecular forces in solids are stronger than those in liquids so that the escaping tendency for surface molecules is higher in liquids. Consequently, surface loss of vapour from liquids by the process of evaporation is more common than surface loss of vapour from solids via sublimation.

In the case of a liquid solvent containing a dissolved solute then molecules of both solvent and solute may show a tendency to escape from the surface and so contribute to the vapour pressure. The relative tendencies to escape will depend not only on the relative numbers of the different molecules in the surface of the solution but also on the relative strengths of the attractive forces between adjacent solvent molecules on the one hand and between solute and solvent molecules on the other hand. Thus, since the intermolecular forces between solid solutes and liquid solvents tend to be relatively strong such solute molecules do not generally escape from the surface of a solution and contribute to the vapour pressure. In other words the solute is non-volatile and the vapour pressure arises solely from the dynamic equilibrium that is set up between the rates of evaporation and condensation of solvent molecules contained in the solution. In a mixture of miscible liquids, i.e. a liquid in liquid solution, the molecules of both components are likely to evaporate and contribute to the overall vapour pressure exerted by the solution.

Ideal solutions; Raoult's Law

The concept of an ideal solution has been introduced in order to provide a model system that can be used as a standard, to which real or non-ideal solutions can be compared. In the model it is assumed that the strengths of all intermolecular forces are identical, i.e. solvent–solvent, solute–solvent and solute–solute interactions are the same and are equal, in fact, to the strength of the intermolecular interactions in either the pure solvent or pure solute. Because of this equality the relative tendencies of solute and solvent molecules to escape from the surface of the solution will be determined only by their relative numbers in the surface. Since a solution is homogeneous by definition then the relative numbers of these surface molecules will be reflected by the relative numbers in the whole of the solution. The latter can be expressed conveniently by the mole fractions of the components because, for a binary solution, i.e. one with two components, $x_1 + x_2 = 1$, where x_1 and x_2 are the mole fractions of the solute and solvent, respectively. Thus, the total vapour pressure (p) exerted by such a binary solution is given by Eqn 3.1:

$$p = p_1 + p_2 = p_1^{\circ}x_1 + p_2^{\circ}x_2 \qquad (3.1)$$

where p_1 and p_2 are the partial vapour pressures exerted above the solution by solute and solvent, respectively, and p_1° and p_2° are the vapour pressures exerted by pure solute and pure solvent, respectively.

If the total vapour pressure of the solution is described by Eqn 3.1 it follows that Raoult's law is obeyed by the system because this law states that the partial vapour pressure exerted by a volatile component in a solution at a given temperature is equal to the vapour pressure of the pure component at the same temperature, multiplied by its mole fraction in the solution, i.e.

$$p_1 = p_1^{\circ}x_1 \qquad (3.2)$$

One of the consequences of the preceding comments is that an ideal solution may be defined as one which obeys Raoult's law. In addition, ideal behaviour should only be expected to be exhibited by real systems comprised of chemically similar components, because it is only in such systems that the condition of equal intermolecular forces between components, that is assumed in the ideal model, is likely to be satisfied. Consequently, Raoult's law is obeyed over an appreciable concentration range by relatively few systems in reality. Mixtures of benzene + toluene, *n*-hexane + *n*-heptane and ethyl bromide + ethyl iodide are commonly mentioned systems that exhibit ideal behaviour, whilst a more pharmaceutically interesting example is provided by binary mixtures of fluorinated hydrocarbons. These latter mixtures are used as propellants in therapeutic aerosols and their approximation to ideal behaviour allows Eqn 3.1 to be used to calculate the total pressure exerted by a given mixture.

Real or non-ideal solutions

The majority of real solutions do not exhibit ideal behaviour because solute–solute, solute–solvent and solvent–solvent forces of interaction are unequal. These inequalities alter the effective concentration of each component so that it cannot be represented by a normal expression of concentration, such as the mole fraction term x that is used in Eqns 3.1 and 3.2. Consequently, deviations from Raoult's law are often exhibited by real solutions and the previous equations are not obeyed in such cases. The equations can be modified, however, by substituting each concentration term (x) by a measure of the effective concentration, which is provided by the so-called *activity* (or *thermodynamic activity*), a. Thus, Eqn 3.2 is converted into Eqn 3.3,

$$p_1 = p_1^{\circ} a_1 \qquad (3.3)$$

which is applicable to all systems whether they be ideal or non-ideal. It should be noted that if a solution exhibits ideal behaviour then $a = x$, whereas $a \neq x$ if deviations from such behaviour are apparent. The ratio of activity/concentration is termed the *activity coefficient* (f) and it provides a measure of the deviation from ideality. (The student is encouraged to study relevant parts of the bibliography for further information on thermodynamic terms such as activity, activity coefficient, free energy and chemical potential.)

If the attractive forces between solute and solvent molecules are weaker than those exerted between the solute molecules themselves or the solvent molecules themselves then the components will have little affinity for each other. The escaping tendency of the surface molecules in such a system is increased when compared with an ideal solution. In other words p_1, p_2 and p are greater than expected from Raoult's law and the thermodynamic activities of the components are greater than their mole fractions, i.e. $a_1 > x_1$ and $a_2 > x_2$. This type of system is said to show a positive deviation from Raoult's law and the extent of the deviation increases as the miscibility of the components decreases. For example, a mixture of alcohol and benzene shows a smaller deviation than the less miscible mixture of water + diethyl ether whilst the virtually immiscible mixture of benzene + water exhibits a very large positive deviation.

Conversely, if the solute and solvent have a strong mutual affinity that results in the formation of a complex or compound then a negative deviation from Raoult's law occurs. Thus, p_1, p_2 and p are lower than expected and $a_1 < x_1$ and $a_2 < x_2$. Examples of systems that show this type of behaviour include chloroform + acetone, pyridine + acetic acid and water + nitric acid.

Even though most systems are non-ideal and deviate either positively or negatively from Raoult's law, such deviations are small when a solution is dilute because the effects of a small amount of solute on interactions between solvent molelcules are minimal. Thus, dilute solutions tend to exhibit ideal behaviour and the activities of their components approximate to their mole fractions, i.e. $a_1 \approx x_1$ and $a_2 \approx x_2$. Conversely, large deviations may be observed when the concentration of a solution is high. Knowledge of the consequences of such marked deviations is particularly important in relation to the distillation of liquid mixtures. For example, the complete separation of the components of a mixture by fractional distillation may not be achievable if large positive or negative deviations from Raoult's law

give rise to the formation of so-called azeotropic mixtures with minimum and maximum boiling points, respectively. Such knowledge is obviously important to the pharmaceutical chemist but is beyond the scope of the present chapter.

IONIZATION OF SOLUTES

Many solutes dissociate into ions if the dielectric constant of the solvent is high enough to cause sufficient separation of the attractive forces between the oppositely charged ions. Such solutes are termed electrolytes and their ionization (or dissociation) has several consequences that are often important in pharmaceutical practice. Some of these consequences are indicated below whilst others that relate to solubilities and dissolution rates are referred to in Chapter 5.

Hydrogen ion concentration and pH

The dissociation of water can be represented by Eqn 3.4:

$$H_2O \rightleftharpoons H^+ + OH^- \qquad (3.4)$$

although it should be realized that this is a simplified representation because the hydrogen and hydroxyl ions do not exist in a free state but combine with undissociated water molecules to yield more complex ions such as H_3O^+ and $H_7O_4^-$.

In pure water the concentrations of H^+ and OH^- ions are equal and at 25 °C both have the values of 1×10^{-7} mol l^{-1}. Since the Lowry–Brönsted theory of acids and bases defines an acid as a substance which donates a proton (or hydrogen ion) it follows that the addition of an acidic solute to water will result in a hydrogen ion concentration that exceeds this value. Conversely, the addition of a base, which is defined as a substance that accepts protons, will decrease the concentration of hydrogen ions.

The hydrogen ion concentration range that can be obtained decreases from 1 mol l^{-1} for a strong acid down to 1×10^{-14} mol l^{-1} for a strong base. In order to avoid the frequent use of low values that arise from this range the concept of pH has been introduced as a more convenient measure of hydrogen ion concentration. pH is defined as the negative logarithm of the hydrogen ion concentration $[H^+]$ as shown by Eqn 3.5:

$$pH = -\log_{10}[H^+] \qquad (3.5)$$

so that the pH of a neutral solution like pure water is 7, because the concentration of H^+ ions (and OH^-) ions $= 1 \times 10^{-7}$ mol l^{-1}, and the pHs of acidic and alkaline solutions will be less or greater than 7, respectively.

pH has several important implications in pharmaceutical practice. For example, in addition to its effects on the solubilities of drugs that are weak acids or bases, as indicated in Chapter 5, pH may have a considerable effect on the stabilities of many drugs, be injurious to body tissues and affect the ease of absorption of drugs from the gastrointestinal tract into the blood (see Chapter 9).

Dissociation (or ionization) constants and pK_a

Many drugs may be classified as weak acids or weak bases which means that in solutions of these drugs equilibria exist between undissociated molecules and their ions. Thus, in a solution of a weakly acidic drug HA the equilibrium may be represented by Eqn 3.6:

$$HA \rightleftharpoons H^+ + A^- \qquad (3.6)$$

although the proton H^+ would be better represented by H_3O^+ because it is always strongly solvated by a water molecule. Similarly, the protonation of a weakly basic drug B can be represented by Eqn 3.7:

$$B + H^+ \rightleftharpoons BH^+ \qquad (3.7)$$

Such equilibria are unlikely to occur in solutions of most salts of strong acids or bases in water because these compounds are completely ionized.

The ionization constant (or dissociation constant) K_a of a weak acid can be obtained by applying the Law of Mass Action to Eqn 3.6 to yield Eqn 3.8:

$$K_a = \frac{[H^+][A^-]}{[HA]} \qquad (3.8)$$

Taking logarithms of both sides of Eqn 3.8 yields

$$\log K_a = \log [H^+] + \log [A^-] - \log [HA]$$

and the signs in this equation may be reversed to give Eqn 3.9:

$$-\log K_a = -\log [H^+] - \log [A^-] + \log [HA] \quad (3.9)$$

The symbol pK_a is used to represent the negative logarithm of the acid dissociation constant K_a in the same way that pH is used to represent the negative logarithm of the hydrogen ion concentration $[H^+]$ and Eqn 3.9 may therefore be rewritten as Eqn 3.10:

$$pK_a = pH + \log [HA] - \log [A^-] \quad (3.10)$$

or

$$pK_a = pH + \log \frac{[HA]}{[A^-]} \quad (3.11)$$

Thus, a general equation, Eqn 3.12, that is applicable to any acidic drug with one ionizable group may be written, where c_u and c_i represent the concentrations of the unionized and ionized species, respectively. This equation is known as the *Henderson–Hasselbalch equation.*

$$pK_a = pH + \log \frac{c_u}{c_i} \quad (3.12)$$

From Eqn 3.7 it can be seen that the acid dissociation constant (K_a) of a protonated weak base is given by Eqn 3.13:

$$K_a = \frac{[H^+][B]}{[BH^+]} \quad (3.13)$$

Taking negative logarithms yields Eqn 3.14:

$$-\log K_a = -\log [H^+] - \log [B] + \log [BH^+] \quad (3.14)$$

or

$$pK_a = pH + \log \frac{[BH^+]}{[B]}$$

The Henderson–Hasselbalch equation for any weak base with one ionizable group may therefore be written as shown by Eqn 3.15:

$$pK_a = pH + \log \frac{c_i}{c_u} \quad (3.15)$$

where c_i and c_u refer to the concentrations of the protonated and unionized species, respectively.

Various analytical techniques, e.g. spectrophotometric and potentiometric methods, may be used to determine ionization constants but the temperature at which the determination is performed should be specified because the values of the constants vary with temperature.

Ionization constants are usually expressed in terms of pK_a values for both acidic and basic drugs and a list of pK_a values for a series of important drugs is given in the *Pharmaceutical Handbook* (1980).

The degree of ionization of a drug in a solution can be calculated from the Henderson–Hasselbalch equations for weak acids and bases (Eqns 3.12 and 3.15, respectively) if the pK_a value of the drug and the pH of the solution are known. Such calculations are particularly useful in determining the degree of ionization of drugs in various parts of the gastrointestinal tract and in the plasma (see Chapter 9). The following examples are therefore related to this type of situation.

1 The pK_a value of aspirin, which is a weak acid, is about 3.5, and if the pH of the gastric contents is 2.0 then from Eqn 3.12

$$\log \frac{c_u}{c_i} = pK_a - pH = 3.5 - 2.0 = 1.5$$

so that the ratio of the concentration of unionized acetylsalicyclic acid to acetylsalicylate anion is given by

$$c_u{:}c_i = \text{antilog } 1.5 = 31.62{:}1$$

2 The pH of plasma is 7.4 so that the ratio of unionized:ionized aspirin in this medium is given by

$$\log \frac{c_u}{c_i} = pK_a - pH = 3.5 - 7.4 = -3.9$$

and

$$c_u{:}c_i = \text{antilog } -3.9 = \text{antilog } \bar{4}.1 = 1.259 \times 10^{-4}{:}1$$

3 The pK_a of the weakly acidic drug sulphapyridine is about 8.0 and if the pH of the intestinal contents is 5.0 then the ratio of unionized:ionized drug is given by

$$\log \frac{c_u}{c_i} = pK_a - pH = 8.0 - 5.0 = 3.0$$

and

$$c_u{:}c_i = \text{antilog } 3.0 = 10^3{:}1$$

4 The pK_a of the basic drug amidopyrine is 5.0, and in the stomach the ratio of ionized:unionized drug is shown from Eqn 3.15 to be given by

$$\log\frac{c_i}{c_u} = pK_a - pH = 5.0 - 2.0 = 3.0$$

and

$$c_i{:}c_u = \text{antilog } 3.0 = 10^3{:}1$$

while in the intestine the ratio is given by

$$\log\frac{c_i}{c_u} = 5.0 - 5.0 = 0$$

and

$$c_i{:}c_u = \text{antilog } 0 = 1{:}1$$

Buffer solutions and buffer capacity

These solutions will maintain a constant pH even when small amounts of acid or alkali are added to the solution. They usually contain mixtures of a weak acid and its salt (i.e. its conjugate base) although mixtures of weak bases and their salts (i.e. their conjugate acids) may be used but suffer from the disadvantage that arises from the volatility of many of the bases.

The action of a buffer solution can be appreciated by considering a simple system such as a solution of acetic acid and sodium acetate in water. The acetic acid, being a weak acid, will be confined virtually to its undissociated form because its ionization will be suppressed by the presence of common acetate ions produced by complete dissociation of the sodium salt. The pH of this solution can be described by Eqn 3.16, which is a rearranged form of Eqn 3.12:

$$pH = pK_a + \log\frac{c_i}{c_u} \qquad (3.16)$$

It can be seen from Eqn 3.16 that the pH will remain constant as long as the logarithm of the ratio c_i/c_u does not change. When a small amount of acid is added to the solution it will convert some of the salt into acetic acid but if the concentrations of both acetate ion and acetic acid are reasonably large then the effect of the change will be negligible and the pH will remain constant. Similarly, the addition of a small amount of base will convert some of the acetic acid into its salt form but the pH will be unaltered if the overall changes in concentrations of the two species are relatively small.

If large amounts of acid or base are added to a buffer then changes in the log c_i/c_u term become appreciable and the pH alters. The ability of a buffer to withstand the effects of acids and bases is an important property from a practical point of view. This ability is expressed in terms of a buffer capacity (β), which is equal to the amount of strong acid or strong base, expressed as moles of H^+ or OH^- ion, required to change the pH of 1 litre of the buffer by 1 pH unit. From the remarks in the previous paragraph it should be obvious that buffer capacity increases as the concentrations of the buffer components increase. In addition, the capacity is also affected by the ratio of the concentrations of weak acid and its salt, maximum capacity (β_{max}) being obtained when the ratio = 1. In such circumstances pH = pK_a of the acid and β_{max} = 0.576 (total buffer concentration).

The components of various buffer systems and the concentrations required to produce different pHs are listed in several reference books, such as the *British Pharmacopoeia* (1980), the *Pharmaceutical Handbook* (1980), the *Merck Index* (1983) and *Documenta Geigy* (1962). When selecting a suitable buffer the pK_a value of the acid should be close to the required pH and the compatibility of its components with other ingredients in the system should be considered. The toxicity of buffer components must also be taken into account if the solution is to be used for medicinal purposes.

Various methods, e.g. pH meters and indicators, may be used to determine the pH of a given solution. These methods are discussed by Carter (1975) in relation to the adjustment of pH of pharmaceutical solutions for injection together with the reasons for such adjustment (see also Chapter 21).

COLLIGATIVE PROPERTIES

When a non-volatile solute is dissolved in a solvent certain properties of the resultant solution are largely independent of the nature of the solute and are determined by the concentration of solute particles. These properties are known as colliga-

tive properties. In the case of a non-electrolyte the solute particles will be molecules but if the solute is an electrolyte then its degree of dissociation will determine whether the particles will be ions only or a mixture of ions and undissociated molecules.

Osmotic pressure

The most important colligative property from a pharmaceutical point of view is referred to as osmotic pressure. However, since all colligative properties are related to each other by virtue of their common dependency on the solute concentration then the remaining colligative properties, which are lowering of vapour pressure of the solvent, elevation of its boiling point and depression of its freezing point, are of pharmaceutical interest because they offer alternative means to osmotic pressure determinations as methods of comparing the colligative properties of different solutions.

The osmotic pressure of a solution is the external pressure that must be applied to the solution in order to prevent it being diluted by the entry of solvent via a process that is known as osmosis. This process refers to the spontaneous diffusion of solvent from a solution of low concentration (or pure solvent) into a more concentrated one through a semipermeable membrane, which separates the two solutions and which is permeable only to solvent molecules.

Since the process occurs spontaneously at constant temperature and pressure the laws of thermodynamics indicate that it will be accompanied by a decrease in the so-called free energy (G) of the system. This free energy may be regarded as the energy available in the system for the performance of useful work and when an equilibrium position is attained then there is no difference between the states that are in equilibrium. The free energy of a solution will depend on the number of moles of solute and solvent and is termed an extensive property of the system as opposed to an intensive property such as temperature, which is independent of the amount of a substance. The rate of increase in free energy of a solution caused by an increase in the number of moles of one component is termed the partial molar free energy ($\bar{G}$) or chemical potential (μ) of that component. For example, the chemical potential of the solvent in a binary solution is given by Eqn 3.17:

$$\left(\frac{\partial G}{\partial n_2}\right)_{T,P,n_1} = \bar{G}_2 = \mu_2 \qquad (3.17)$$

where the subscripts outside the bracket on the left hand side indicate that temperature, pressure and amount of component 1 (the solute in this case) remain constant.

Because only solvent can pass across the semipermeable membrane the driving force for osmosis arises from the inequality of the chemical potentials of the solvent on opposing sides of the membrane. Thus the direction of osmotic flow is from the dilute solution (or pure solvent), where the chemical potential of the solvent is highest because there are more moles of it, into the concentrated solution, where the number of moles and, consequently, the chemical potential of the solvent is reduced by the presence of more solute.

The chemical potential of the solvent in the more concentrated solution can be increased by forcing its molecules closer together under the influence of an externally applied pressure. Osmosis can be prevented, therefore, by such means, hence the definition of osmotic pressure.

The relationship between osmotic pressure (π) and concentration of a non-electrolyte is given for dilute solutions, which may be assumed to exhibit ideal behaviour, by the van't Hoff equation (Eqn 3.18):

$$\pi V = n_2 RT \qquad (3.18)$$

where V is the volume of solution, n_2 is the number of moles of solute, T is the thermodynamic temperature and R is the gas constant. This equation, which is similar to the ideal gas equation, was derived empirically but it does correspond to a theoretically derived equation if approximations based on low solute concentrations are taken into account.

If the solute is an electrolyte Eqn 3.18 must be modified in order to allow for the effect of ionic dissociation, because this will increase the number of particles in the solution. This modification is achieved by insertion of the van't Hoff correction factor (i) to give

$$\pi V = i n_2 RT \qquad (3.19)$$

$$\text{where } i = \frac{\text{observed colligative property}}{\text{colligative property expected if dissociation did not occur}}$$

Osmolality and osmolarity

The amount of osmotically active particles in a solution is sometimes expressed in terms of osmoles or milliosmoles (1 osmol = 1×10^3 mosmol) and these particles may be either molecules or ions. The concentration of a solution may therefore be expressed in terms of its osmolality or its osmolarity, where osmolality is the number of osmoles per kilogram of water and osmolarity is the number of osmoles per litre of solution.

Iso-osmotic solutions

If two solutions are separated by a perfect semipermeable membrane, i.e. a membrane which is permeable only to solvent molecules, and no net movement of solvent occurs across the membrane then the solutions are said to be iso-osmotic and will have equal osmotic pressures.

Isotonic solutions

Biological membranes do not always function as perfect semipermeable membranes and some solute molecules as well as water are able to pass through them. However, if two iso-osmotic solutions remain in osmotic equilibrium when separated by a biological membrane they may be described as being isotonic with respect to that particular membrane.

The consequences of deviation from isotonicity (i.e. hypo- and hypertonicity) with serum in relation to the formulation of solutions for intravenous administration are described in Chapter 21. Reasons for adjusting the tonicity of formulations intended for other parenteral routes of administration are given in the same chapter.

DIFFUSION IN SOLUTION

By definition the components of a solution form a single phase, which is homogeneous. This homogeneity arises from the process of diffusion, which occurs spontaneously and is consequently accompanied by a decrease in the free energy (G) of the system. Diffusion may be defined as the spontaneous transference of a component from a region in the system where it has a high chemical potential into a region where its chemical potential is lower. Although such a gradient in chemical potential provides the driving force for diffusion the laws that describe this phenomenon are usually expressed in terms of concentration gradients. For example, Fick's first law, which indicates that the rate of diffusion is proportional to the concentration gradient, may be expressed by Eqn 3.20:

$$\mathcal{J} = \frac{\mathrm{d}m}{\mathrm{d}t} = -\mathrm{D}\frac{\mathrm{d}C}{\mathrm{d}x} \tag{3.20}$$

where $\mathcal{J}$, the flux of a component, is given by the rate of diffusion of the component expressed in terms of amount ($\mathrm{d}m$) transported in time ($\mathrm{d}t$) across a plane of unit area and $\mathrm{d}C/\mathrm{d}x$ is the concentration gradient. The negative sign on the right hand side is necessary because diffusion occurs in the opposite direction to that of increasing concentration, i.e. $\mathrm{d}C/\mathrm{d}x$ is negative. D is known as the *diffusion coefficient* and is assumed to have a constant value for a particular system at a given temperature. This assumption is only strictly true at infinite dilution and D may therefore exhibit some concentration dependency. The dimensions of D are area per unit time, e.g. $\mathrm{cm^2\ s^{-1}}$. In a given solvent the value of D decreases as the size of the diffusing solute molecule increases. In water, for example, D is of the order of $2 \times 10^{-5}\ \mathrm{cm^2\ s^{-1}}$ for solutes with molecular weights of approximately 50 and it decreases to about $1 \times 10^{-6}\ \mathrm{cm^2\ s^{-1}}$ when the molecular weight increases to a few thousand.

The most common explanation of the mechanism of diffusion in solution is based on the lattice theory of the structure of liquids. (It should be noted that other approaches to liquid structures have been considered, see, for example, Eyring *et al.* (1971) and Barker and Henderson (1972).) Various lattice theories have been proposed (Barker, 1963) the one receiving most attention being the significant structure theory of Eyring and his collaborators (e.g. Eyring and Jhon, 1969).

Lattice theories postulate that liquids have crystalline or quasicrystalline structures. The concept of a crystal type of lattice is only intended to provide a convenient starting point and should not be interpreted as a suggestion that liquids possess rigid structures. The theories also postulate that a reasonable proportion of the volume occupied by the liquid is, at any moment, empty, i.e. there are 'holes' in the liquid lattice network, which constitute the so-called free volume of the liquid. Such a hole is produced when the kinetic energy (the pressure), which tends to make a region expand, is balanced by the opposing potential energy density (the internal pressure), which tends to bring about collapse of the hole.

Diffusion can therefore be regarded as the process by which solute molecules move from hole to hole within a liquid lattice. In order to achieve such movement a solute molecule must acquire sufficient kinetic energy at the right time so that it can break away from any bonds that tend to anchor it in one hole and then jump into an adjacent hole. If the average distance of each jump is δ cm and the frequency with which the jumps occur is ϕ s^{-1} then the diffusion coefficient (D) is given by

$$D = \frac{\delta^2\phi}{6} \text{ cm}^2 \text{ s}^{-1} \qquad (3.21)$$

The value of δ for a given solute is unlikely to alter very much from one liquid to another. Differences in the diffusion coefficient of a substance in solution in various solvents arise mainly from changes in jump frequency (ϕ), which is determined, in turn, by the free volume or looseness of packing in the solvent.

When the size of the solute molecules is not appreciably larger than that of the solvent molecules then Stein (1962) has shown that the diffusion coefficient of the former is related to its molecular weight (M) by the relationship

$$DM^{\frac{1}{2}} = \text{constant} \qquad (3.22)$$

When the solute is much greater in size than the solvent, diffusion arises largely from transport of solvent molecules in the opposite direction and the relationship becomes

$$DM^{\frac{1}{3}} = \text{constant} \qquad (3.23)$$

This latter equation agrees with the Stokes–Einstein equation (3.24) for the diffusion of spherical particles that are larger than surrounding liquid molecules, since the mass (m) of a spherical particle is proportional to the cube of its radius (r), i.e. $r \propto m^{\frac{1}{3}}$ and it follows from Eqn 3.23 that $Dm^{\frac{1}{3}}$ and consequently Dr are constants for such a system. The Stokes–Einstein equation is usually written in the form

$$D = \frac{kT}{6\pi r\eta} \qquad (3.24)$$

where k is the Boltzmann constant, T is the thermodynamic temperature and η is the viscosity of the liquid. The appearance of a viscosity term in this type of equation is not unexpected because the reciprocal of viscosity, which is known as the fluidity of a liquid, is proportional to the free volume in a liquid. Thus, jump frequency (ϕ) and diffusion coefficient (D) will increase as the viscosity of a liquid decreases or as the number of holes in its structure increases.

The experimental determination of diffusion coefficients of solutes in liquid solvents is not easy because the effects of other factors that may influence the movement of solute in the system, e.g. temperature and density gradients, mechanical agitation and vibration, must be eliminated. Students are recommended to consult the bibliography for descriptions of experimental techniques.

REFERENCES AND BIBLIOGRAPHY

Barker, J. A. (1963) *Lattice Theories of the Liquid State*, Pergamon Press, Oxford.

Barker, J. A. and Henderson, D. (1972) *Ann. Rev. phys. Chem.*, **23**, 439.

Beckett, A. H. and Stenlake, J. B. (1975) *Practical Pharmaceutical Chemistry Part 1: General Pharmaceutical Chemistry*, 3rd Edn, Athlone Press, London.

British Pharmacopoeia (1980) HMSO, London.

Carstensen, J. T. (1972) *Theory of Pharmaceutical Systems*, Vol. 1. *General Principles*, Academic Press, London.

Carter, S. J. (ed.) (1975) *Dispensing for Pharmaceutical Students*, 12th edn. Pitman, London.

Documenta Geigy (1962) 6th edn (Ed. K. Diem). Geigy Pharmaceutical Company, Manchester.

Eyring, H., Henderson, D. and Jost, W. (1971) *Physical Chemistry, An Advanced Treatise*, Volume VIIIA, *Liquid State*, Academic Press, London.
Eyring, H. and Jhon, M. S. (1969) *Significant Liquid Structure*, Wiley, New York.
Florence, A. T. and Attwood, D. (1981) *Physicochemical Principles of Pharmacy*, Macmillan Press Ltd, London.
Hildebrand, J. H., Prausnitz, J. M. and Scott, R. L. (1970) *Regular and Related Solutions: the Solubility of Gasses, Liquids and Solids*, Van Nostrand Reinhold, New York.
Merck Index (1983) 10th edn (Ed. M. Windholz), Merck.
Pharmaceutical Handbook (1980) 19th edn (Ed. A. Wade), The Pharmaceutical Press, London.
Price, N. C. and Dwek, R. A. (1979) *Principles and Problems in Physical Chemistry for Biochemists*, 2nd edn, Clarendon Press, Oxford.
Rowlinson, J. S. and Swinton, F. L. (1982) *Liquids and Liquid Mixtures*, 3rd edn, Butterworth Scientific, London.
Stein, W. D. (1962) In: *Comprehensive Biochemistry* (Ed. M. Florkin and E. Stotz), Vol. 2, Chapter III, Elsevier, Amsterdam.
Wallwork, S. C. and Grant, D. J. W. (1977) *Physical Chemistry for Students of Pharmacy and Biology*, 3rd edn, Longman, London.
Williams, V. R., Mattice, W. L. and Williams, H. B. (1978) *Basic Physical Chemistry for the Life Sciences*, 3rd edn, W.H. Freeman and Co., San Francisco.

Disperse systems

DISPERSE SYSTEMS

COLLOID SCIENCE

Preparation of colloids
- *Lyophilic colloids*
- *Lyophobic colloids*
- *Dispersion methods*
  - ***Colloid mills***
  - ***Ultrasonic treatment***
- *Condensation methods*
- *Dialysis*
  - ***Ultrafiltration***
  - ***Electrodialysis***
  - ***Pharmaceutical applications of dialysis***

Properties of colloids

Kinetic properties
- *Brownian motion*
- *Diffusion*
- *Sedimentation*
  - ***Sedimentation velocity***
  - ***Sedimentation equilibrium***
- *Osmotic pressure*
- *The Donnan membrane effect*
- *Viscosity*

Optical properties
- *Light scattering*
- *Ultramicroscope*
- *Electron microscope*

Electrical properties
- *Electrical properties of interfaces*
  - ***Ion dissolution***
  - ***Ionization***
  - ***Ion adsorption***
- *The electrical double layer*
- *Electrokinetic phenomena*
  - ***Electrophoresis***
  - ***Other electrokinetic phenomena***

Physical stability of colloidal systems
- *Stability of lyophobic systems*
  - ***DLVO theory***
  - ***Repulsive forces between particles***
  - ***Attractive forces between particles***
  - ***Total potential energy of interaction***
- *Stability of lyophilic systems*
  - ***Coacervation and microencapsulation***
  - ***Effect of addition of macromolecular material to lyophobic colloidal sols***
- *Steric stabilization (protective colloid action)*

GELS
- *Types of gel*
- *Applications*

SURFACE-ACTIVE AGENTS

Micellization

Physical properties of surface active agent solutions
- *Surface properties*
- *Electrical conductivity*
- *Solubility: the Krafft point*
- *Light scattering*
- *Other methods of determining CMCs*

Solubilization
- *Applications of solubilization*
- *Solubilization and drug stability*

Detergency

COURSE DISPERSE SYSTEMS

SUSPENSIONS

The controlled flocculation approach to suspension formulation

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

Stability of non-aqueous dispersions

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.

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)

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

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

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

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

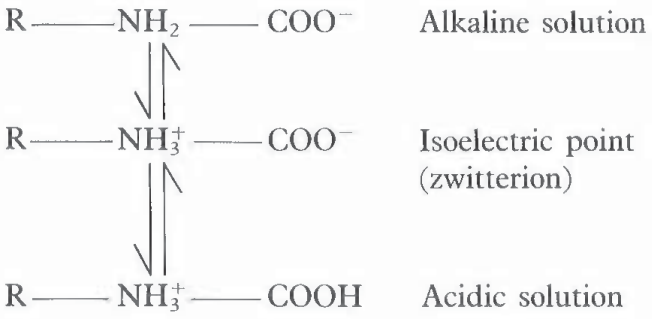
Electrical properties of interfaces

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

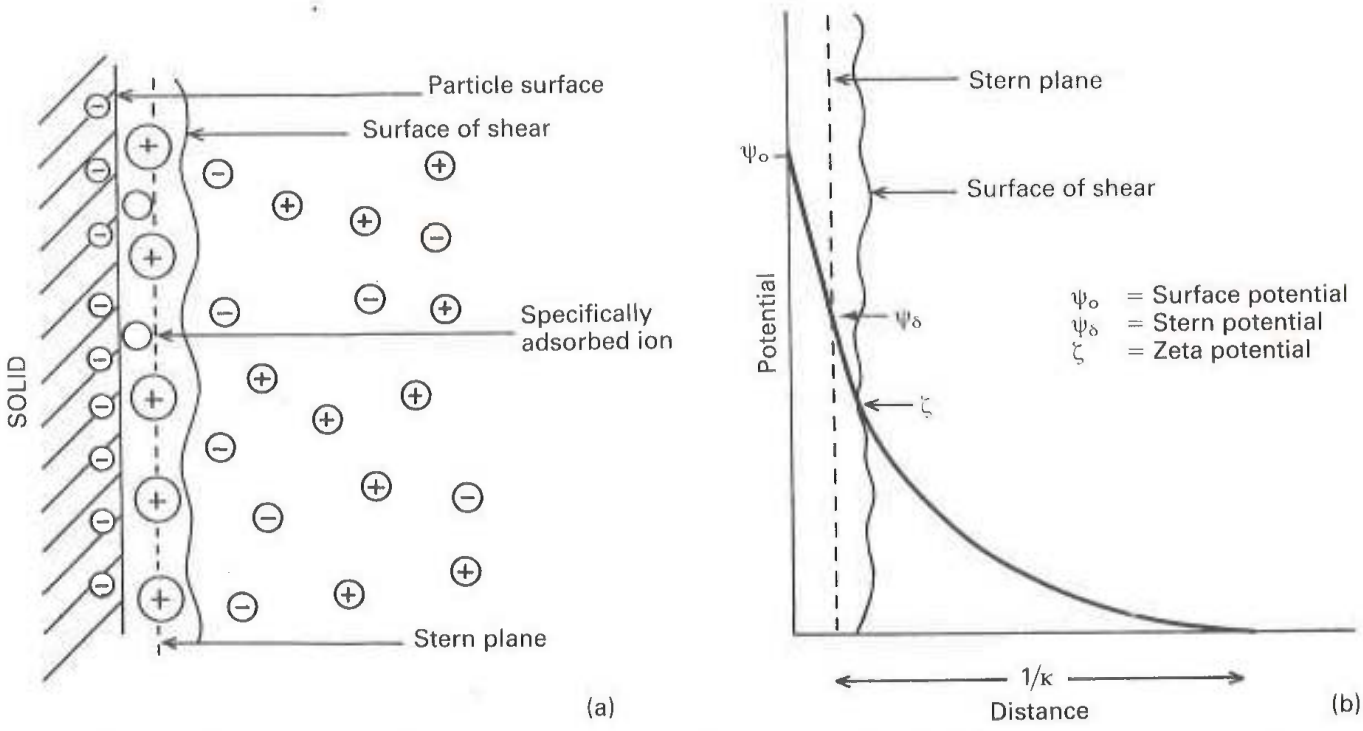


Fig. 6.1 The electric double layer: (a) schematic representation (b) changes in potential with distance from particle surface

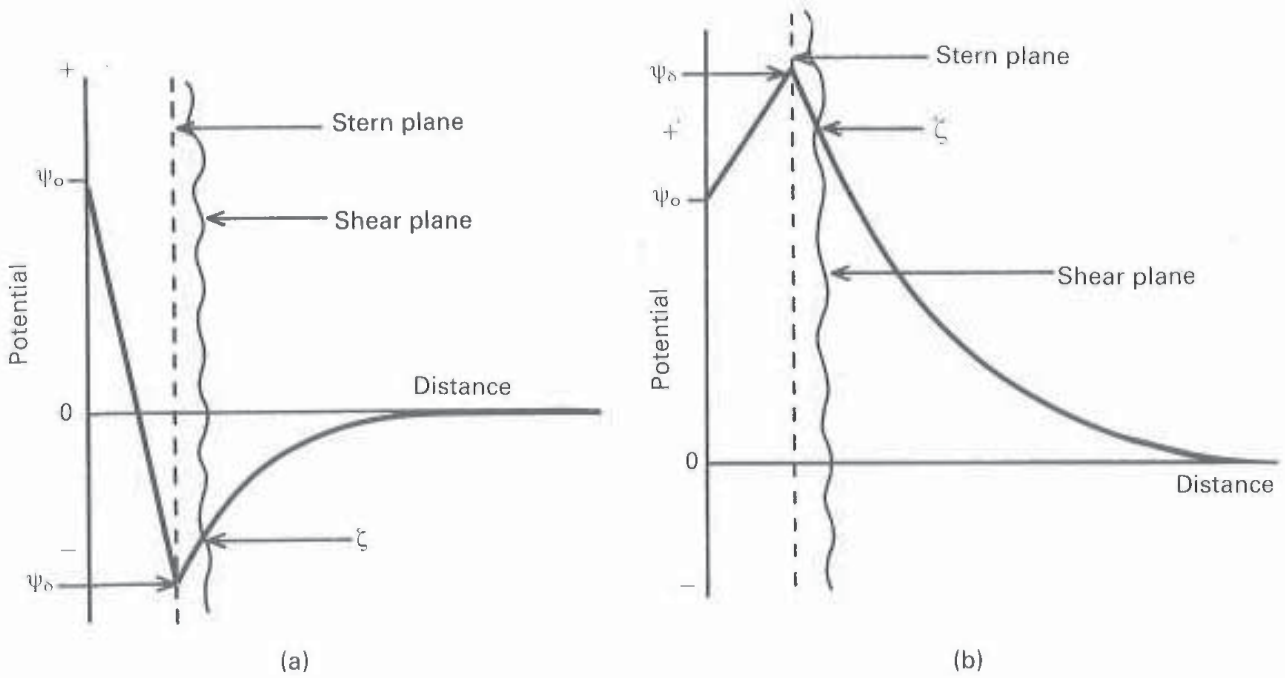


Fig. 6.2 Changes in potential with distance from solid surface: (a) reversal of charge sign of Stern potential ψ_δ, due to adsorption of surface-active or polyvalent counter ion, (b) increase in magnitude of Stern potential ψ_δ, due to adsorption of surface active co-ions

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 $4 \times 10^{-8}\ m^2\ s^{-1}\ V^{-1}$. 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

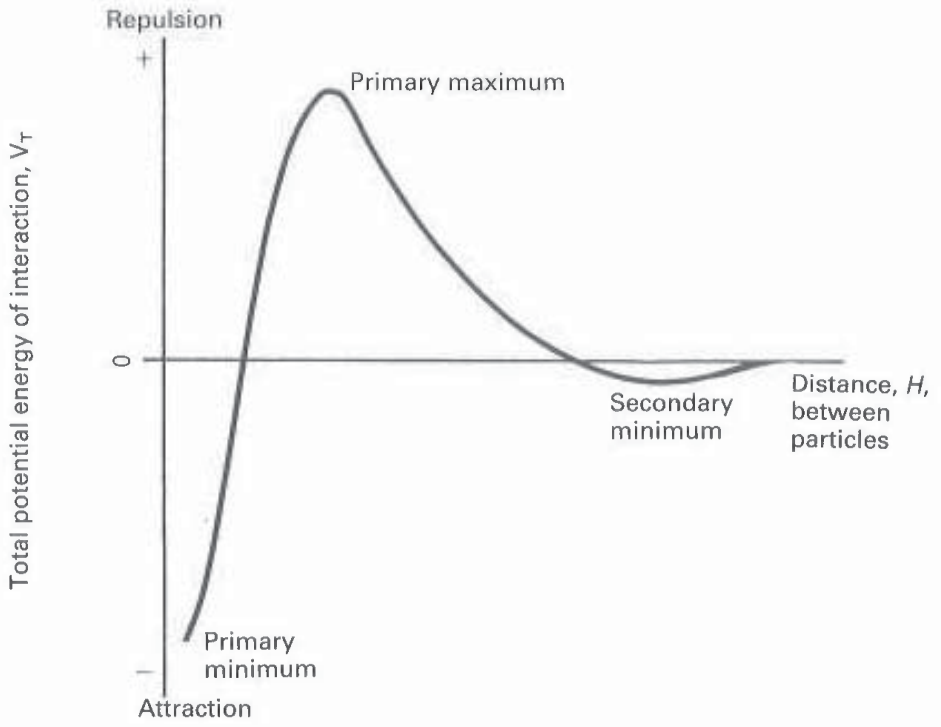


Fig. 6.3 Schematic curve of total potential energy of interaction V_T, versus distance of separation, H, for two particles. $V_T = V_R + V_A$

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

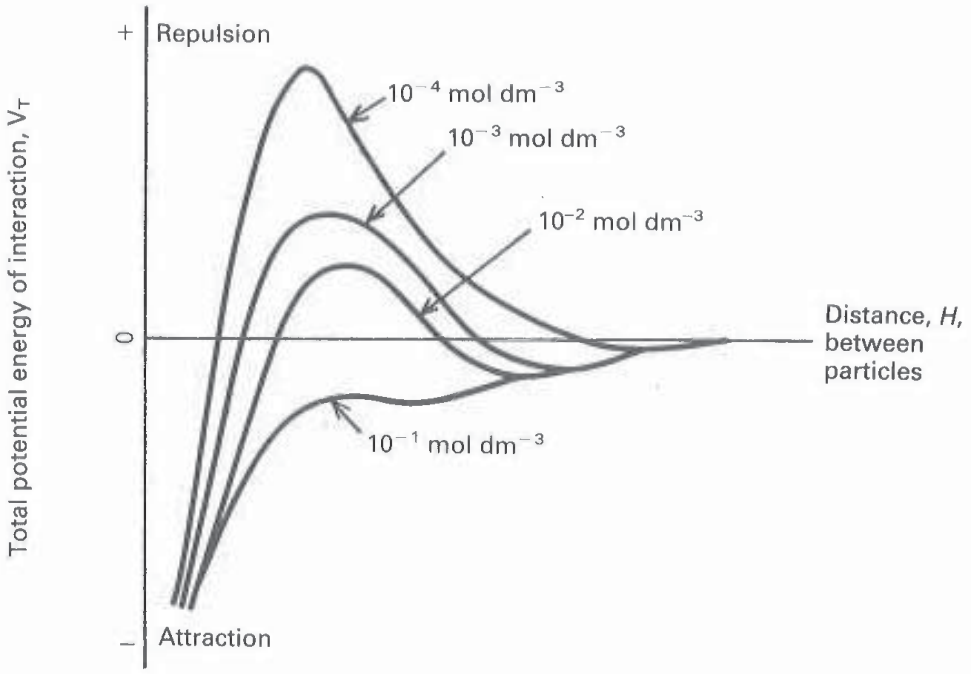


Fig. 6.4 Schematic curves of total potential energy of interaction V_T, versus distance of separation, H, showing the effect of adding electrolyte at constant surface potential

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-

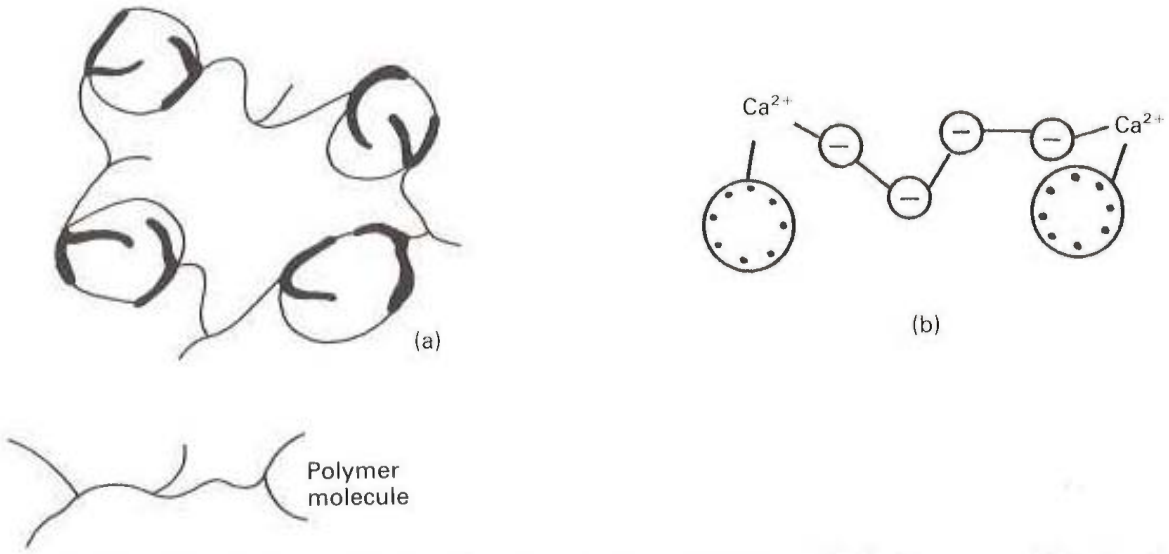


Fig. 6.5 Diagram of flocs formed (a) by polymer bridging and (b) polyelectrolyte bridging in the presence of divalent ions of opposite charge

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

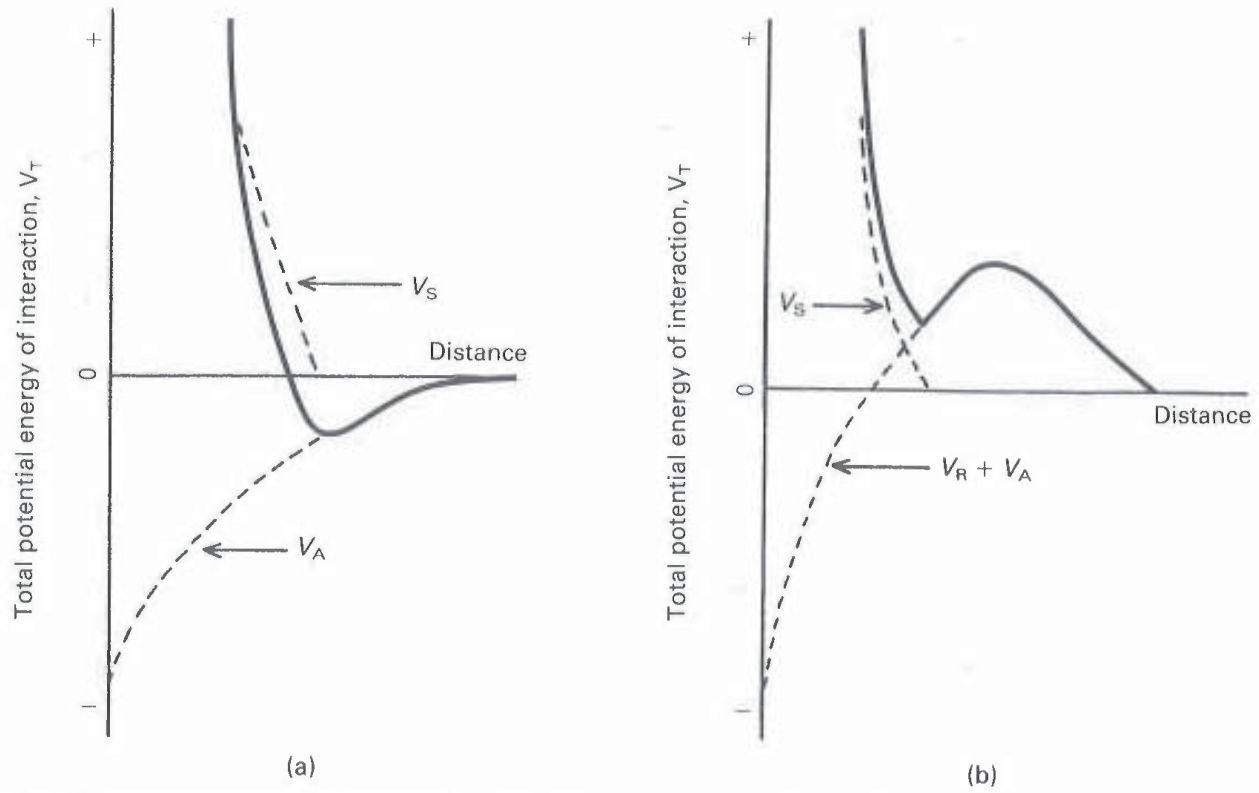


Fig. 6.6 Schematic curves of the total potential energy of interaction versus distance for two particles, showing the effect of the steric stabilization term V_S: (a) in the absence of electrostatic repulsion, the solid line representing $V_T = V_A + V_S$, (b) in the presence of electrostatic repulsion,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

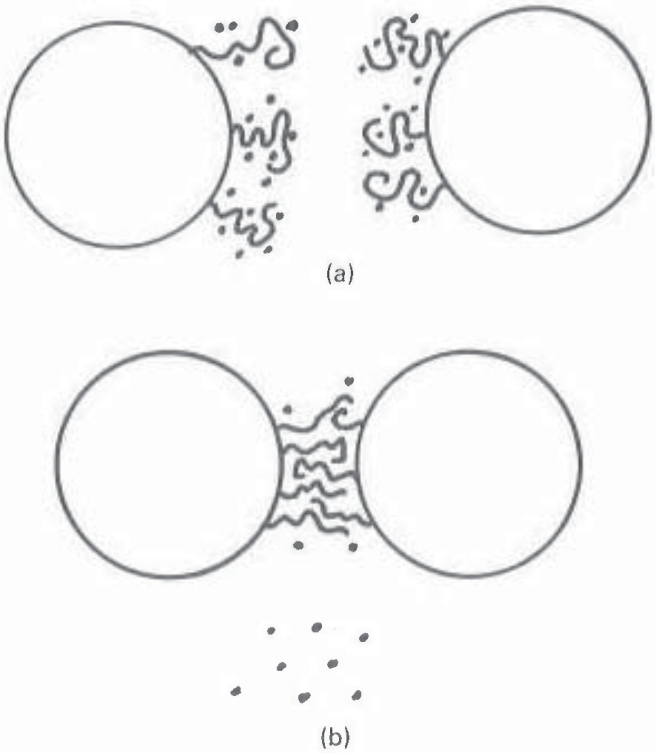


Fig. 6.7 Enthalpic stabilization: (a) particles with stabilizing polyoxyethylene chains and H-bonded water molecules, (b) stabilizing chains overlap, water molecules released $\rightarrow + \Delta H$

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

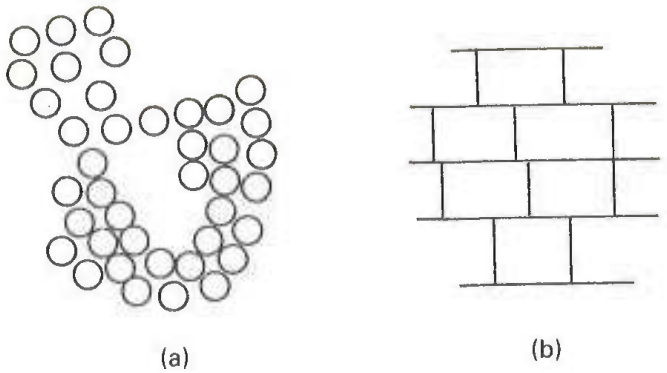


Fig. 6.8 Gel structure: (a) flocculated lyophobic sol, e.g. aluminium hydroxide, (b) 'card house' floc of clays, e.g. bentonite

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)	$CH_3(CH_2)_{15}$——$N^+(CH_3)_2Br^-$
Dodecyl pyridinium iodide	$CH_3(CH_2)_{11}$—C$_6$H$_4$—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	$C_{17}H_{33}$——$COOCH_2$
Ampholytic	
N-dodecyl alanine	$CH_3(CH_2)_{11}$——$NH_2^+.CH_2.CH_2.COO^-$
Lecithin	$C_{17}H_{35}$——$COO.CH_2$ $C_{17}H_{35}$——$COO.CH$ 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.

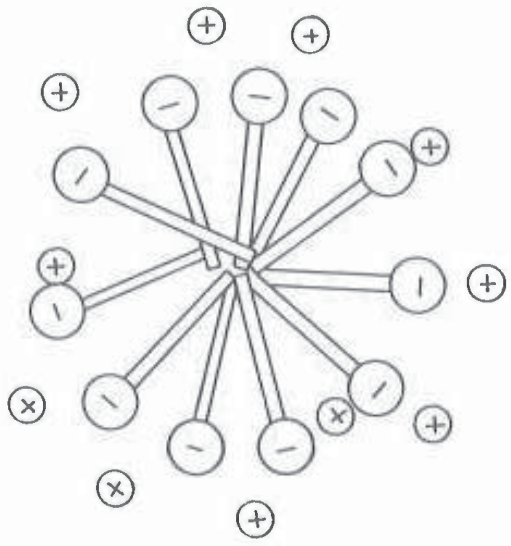


Fig. 6.9 Schematic diagram of the Hartley spherical micelle

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.

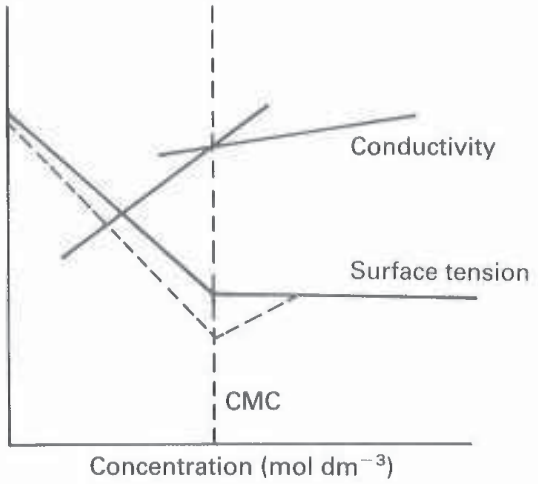


Fig. 6.10 Diagram of variation of conductivity and surface tension with concentration of an ionic surface-active agent such as sodium dodecyl sulphate

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.

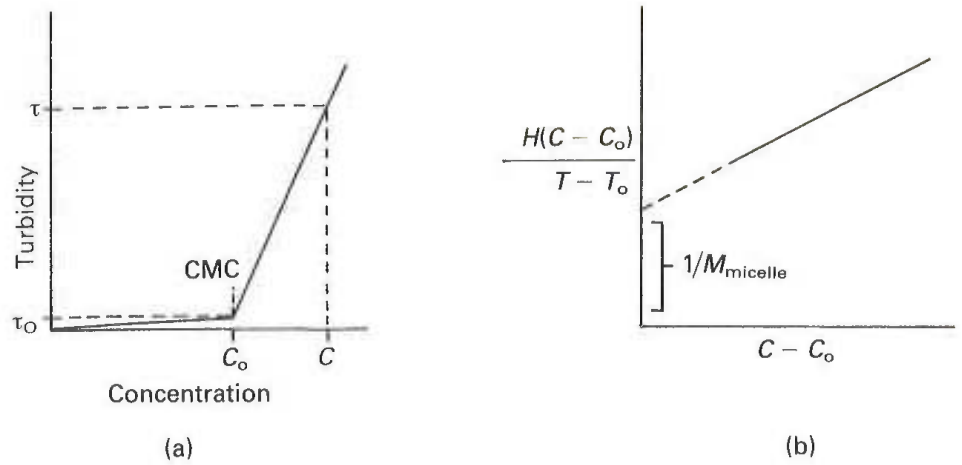


Fig. 6.11 Light scattering by solutions of surface-active agents: (a) turbidity versus concentration, (b) plot of the modified Debye equation for estimation of micellar size

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

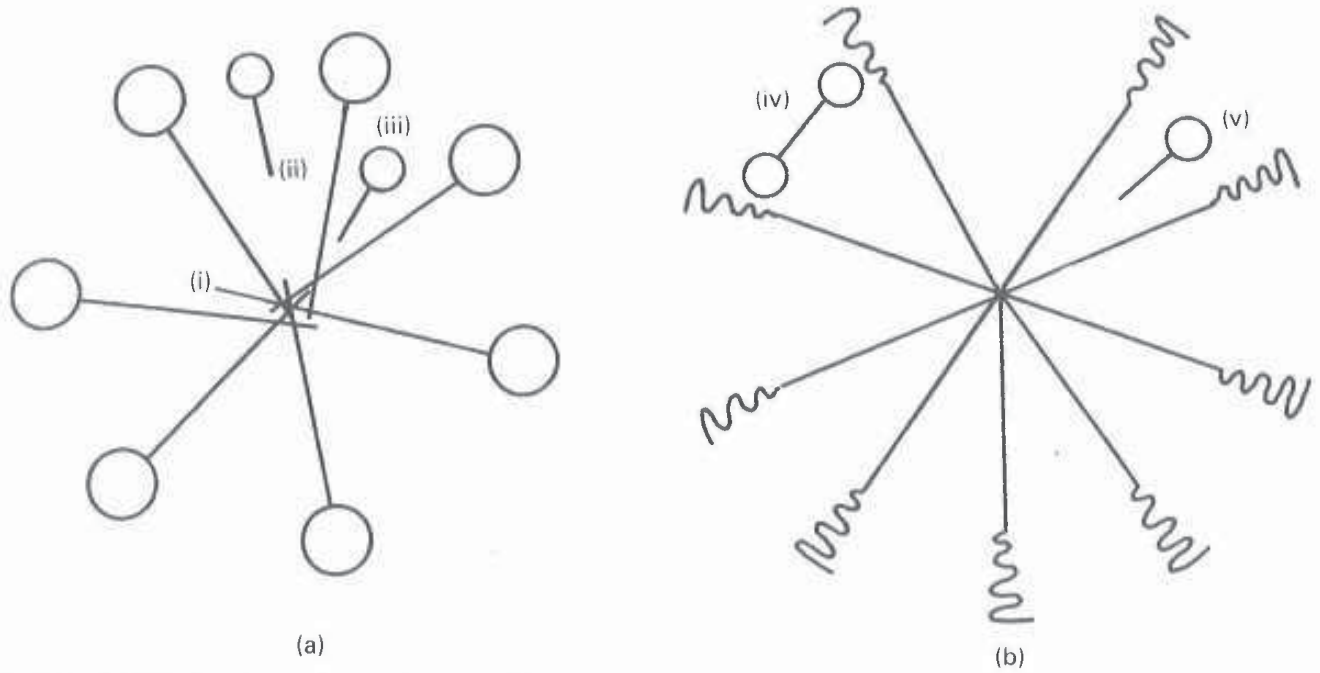


Fig. 6.12 Solubilization in micelles of (a) ionic and (b) non-ionic polyethoxylated surface active agents. See text for details

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.

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

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.

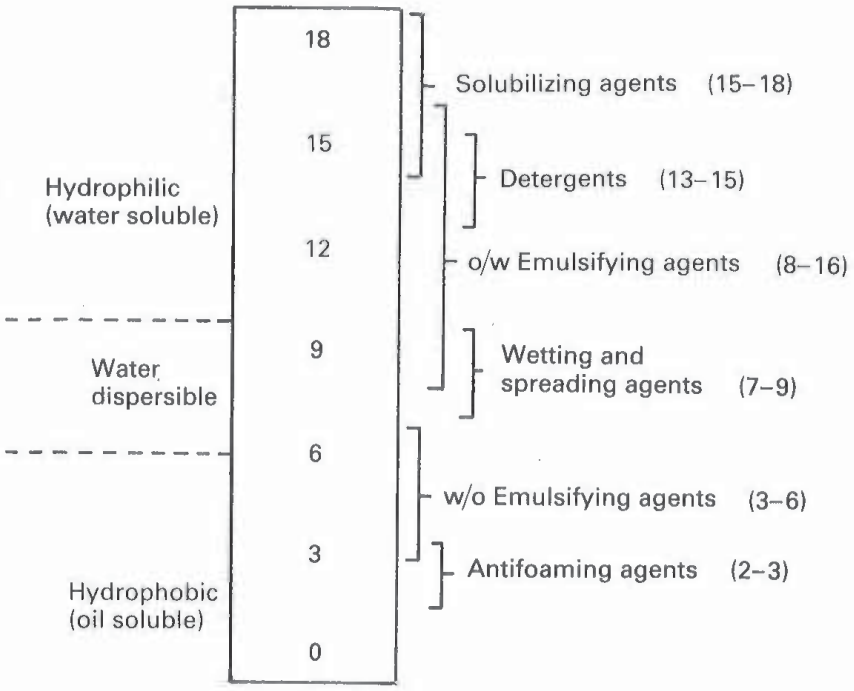


Fig. 6.13 HLB scale showing classification of surfactant function

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.

REFERENCES

Adam, N. K. (1970) *The Physics and Chemistry of Surfaces*, Dover Edition, London.

Carrigan, P. G. and Bates, T. R. (1973) Biopharmaceutics of drugs administered in lipid containing dosage forms I. GI adsorption of griseofulvin from an o/w emulsion to the rat. *J. Pharm. Sci.*, **62**, 1476–1479.

Carter, S. J. (1975) *Dispensing for Pharmaceutical Students*, Pitman, London.

Davies, J. T. and Rideal, E. K. (1963) *Interfacial Phenomena*, 2nd edn, Academic Press, London.

Elworthy, P. H., Florence, A. T. and Macfarlane, C. B. (1968) *Solubilization by Surface Active Agents*, Chapman and Hall, London.

Evans, R. and Napper, D. H. (1973) Steric stabilization II Generalization of Fischers' solvency theory. *Kolloid. Z.u.Z. Polymere*, **251**, 329–336.

Florence, A. T. and Rogers, J. A. (1971) Emulsion stabilization by nonionic surfactants: experiment and theory. *J. Pharm. Pharmacol.*, **23**, 153–169.

Kayes, J. B. (1977a) Pharmaceutical suspensions: relation between zeta potential, sedimentation volume and suspension stability. *J. Pharm. Pharmacol.*, **29**, 199–204.

Kayes, J. B. (1977b) Pharmaceutical suspensions: micro electrophoretic properties. *J. Pharm. Pharmacol.*, **29**, 163–168.

Law, S. L. and Kayes, J. B. (1983) Adsorption of nonionic water soluble cellulose polymers at the solid water interface and their effect on suspension stability. *Int. J. Pharmaceut.*, **15**, 251–260.

Parkinson, C. and Sherman, P. (1972) Phase inversion temperature as an accelerated method for evaluating emulsion stability. *J. Colloid interface Sci.*, **41**, 328–330.

Rawlins, D. A. and Kayes, J. B. (1980) Steric stabilization of suspensions drug. *Dev. ind. Pharm.*, **6**(5), 427–440.

Rawlins, D. A. and Kayes, J. B. (1983) Pharmaceutical suspensions III. The redispersibility of suspensions. *Int. J. Pharmaceut.*, **13**, 171–181.

Schulman, J. H. and Cockbain, E. G. (1940) Molecular interactions at oil–water interfaces I. Molecular complex formation and the stability of oil-in-water emulsions. *Trans. Faraday. Soc.*, **36**, 651–660.

Shaw, D. J. (1980) *Introduction to Colloid and Surface Chemistry*, 3rd edn, Butterworths, London.

Sherman, P. (1968) *Emulsion Science*, Academic Press, London.

Sheth, P. B. and Parrot, E. L. (1967) Hydrolysis of solubilized esters. *J. Pharm. Sci.*, **56**, 983–986.
Shotton, E. and White, R. (1963) In *Rheology of Emulsions* (Ed. P. Sherman), Pergamon Press, Oxford.
Vincent, B. (1973) Non-aqueous systems. In: *Colloid Science*, Vol. I Chapter 7, The Chemical Society, London.
Wiersema, P. H., Loeb, A. L. and Overbeek, J. Th. G. (1966) Calculation of electrophoretic mobility of a spherical colloid particle. *J. Colloid interface Sci.*, **22**, 78–99.

BIBLIOGRAPHY

Ackers, R. J. (Ed.) (1976) *Foams*, Academic Press, London.
Adam, N. K. (1970) *The Physics and Chemistry of Surfaces*, Dover Edition, London.
Adamson, A. W. (1982) *Physical Chemistry of Surfaces*, 4th edn, Wiley, New York.
Davies, J. T. and Rideal, E. K. (1963) *Interfacial Phenomena*, 2nd edn, Academic Press, London.
Elworthy, P. H., Florence, A. T. and Macfarlane, C. B. (1968) *Solubilization by Surface Active Agents*, Chapman and Hall, London.
Florence, A. T. and Attwood, D. (1981) *Physicochemical Principles of Pharmacy*, Macmillan, London.
Kruyt, H. R. (Ed.) *Colloid Science*. Vol. I *Irreversible Systems* (1952), Vol. II *Reversible Systems* (1949), Elsevier, Amsterdam.
M.T.P. International Review of Science (1972) Physical Chemistry, Series One. Vol. 7 *Surface Chemistry and Colloids*, M. Kerker (Ed.), Chapter 4, Aggregation in Surfactant Systems, Butterworths, London.
Ottewill, R. H. (1973) Steric stabilization. In: *Colloid Science*, Vol. I, Chapter 5 Particulate Dispersions, The Chemical Society, London.
Parfitt, G. D. (1973) *Dispersions of Powders in Liquids*, 2nd edn, Applied Science.
Shaw, D. G. (1980) *Introduction to Colloid and Surface Chemistry*, 3rd edn, Butterworths, London.
Sherman, P. (1968) *Emulsion Science*, Academic Press, London.
Smith, A. L. (Ed.) (1976) *Theory and Practice of Emulsion Technology*, Academic Press, London.
Tanford, C. (1980) *The Hydrophobic Effect. Formation of Micelles and Biological Membranes*, 2nd edn, wiley, New York.
Van Olphen, H. (1977) *An Introduction to Clay Colloid Chemistry*, 2nd edn, Wiley, New York.

Introduction to biopharmaceutics

Before the reader can appreciate the meaning and clinical significance of *biopharmaceutics*, it is necessary to introduce the concept of drug bioavailability.

The concept of bioavailability

The therapeutic response of a drug is normally dependent on an adequate concentration of the drug being achieved and then maintained at the site or sites of action of the drug. In the case of systemically acting drugs (i.e. drugs that reach these sites via the systemic circulation) it is generally accepted for clinical purposes that a dynamic equilibrium exists between the concentration of drug at its site(s) of action and the concentration of drug in blood plasma. An important consequence of this dynamic equilibrium is that it permits a therapeutically effective concentration of drug to be achieved at its site(s) of action by adjustment of the concentration of drug in blood plasma. Strictly speaking, the concentration of drug in plasma water (i.e. protein-free plasma) is a more accurate index of drug concentration at the site(s) of action than is the concentration of drug in whole plasma since a drug may often bind in a reversible manner to plasma protein. Only drug which is unbound (i.e. dissolved in plasma water) can pass out of the plasma through the capillary endothelium and reach other body fluids and tissues and hence its site(s) of action. Drug concentration in whole blood is also not considered to be an accurate indirect index of the concentration of drug at its site(s) of action since drug can bind to and enter blood cells. However, to measure the concentration of an unbound drug in plasma water

requires more complex and sensitive assay methods than to measure the total concentration of both unbound and bound drug in total plasma. Thus, for clinical purposes, drug concentration in blood plasma is usually measured and is regarded as an index of drug concentration at the site(s) of action of the drug and of the clinical effects of the drug. However, it should be realized that this is a simplification and may not always be valid. Indeed one should not draw inferences about the clinical effects of a drug from its plasma concentration until it has been established that the two are consistently correlated. For simplicity, in the remainder of this chapter, it has been assumed that the plasma drug concentration is directly proportional to the clinical effect of that drug.

The concentration of drug in blood plasma depends on numerous factors. These include the relative amount of an administered dose that enters the systemic circulation, the rate at which this occurs, the rate and extent of distribution of the drug between the systemic circulation and other tissues and fluids and the rate of elimination of the drug from the body.

A schematic representation of some of the factors which can influence the concentration of a drug in the blood plasma and also at its site(s) of action is shown in Fig. 8.1.

Apart from the intravenous route of drug administration, where a drug is introduced directly into the blood circulation, all other routes of administering systemically acting drugs involve the absorption of drug from the place of administration into the blood. Drug must be absorbed in a sufficient quantity and at a sufficient rate in order to achieve a certain blood plasma concentration which, in turn, will produce an appropriate concentration of drug at its site(s) of action to elicit the desired therapeutic response.

It follows that there are two aspects of drug absorption which are important in clinical practice, namely, the rate and the extent to which the administered dose is absorbed. Simply because a certain dose of a drug is administered to a patient, there is no guarantee (except for intravenous administration) that all of that dose will reach the systemic circulation. The fraction of an administered dose of drug that reaches the systemic circulation in unchanged form is known as the *bioavailable dose*. The relative amount of an administered dose of a particular drug which reaches the systemic circulation intact and the rate

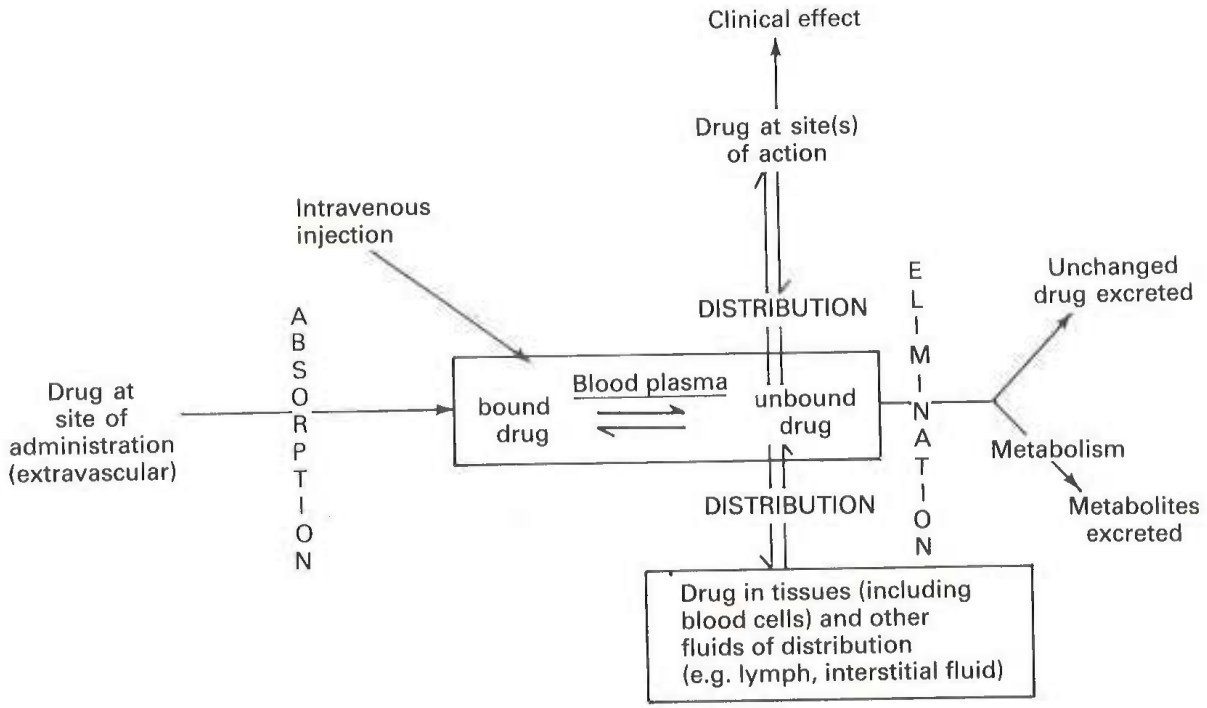


Fig. 8.1 Schematic representation of drug absorption, distribution and elimination

at which this occurs is known as the *bioavailability* of that drug. Bioavailability is thus concerned with the quantity and rate at which the *intact* form of a particular drug appears in the systemic circulation following administration of that drug. The bioavailability exhibited by a drug is thus very important in determining whether a therapeutically effective concentration is achieved at the site(s) of action of the drug.

In defining bioavailability in these terms it is assumed that intact drug is the therapeutically active form of the drug. This definition of bioavailability would not be valid in the case of a pro-drug, whose therapeutic action normally depends on it being converted into its therapeutically active form prior to or on reaching the systemic circulation. It should also be noted that in the context of bioavailability, the term systemic circulation refers primarily to venous blood (excluding the hepatic portal blood during the absorption phase) and arterial blood which carries the intact drug to the tissues.

Hence according to the definition of bioavailability an administered dose of a particular drug in an oral dosage form will be 100% bioavailable only if the drug is completely released from the dosage form into solution in the gastrointestinal fluids. The released drug must also be completely stable in solution in the gastrointestinal fluids and all of the drug must pass through the gastrointestinal barrier into the mesenteric circulation without being metabolized. Finally, all of the absorbed drug must pass into the systemic circulation without being metabolized on passing through the liver. Thus any factor which adversely effects either the release of the drug from the dosage form, its dissolution in the gastrointestinal fluids, its stability in the gastrointestinal fluids, its permeation through and stability in the gastrointestinal barrier or its stability in the hepatic portal circulation will influence the bioavailability exhibited by that drug from the dosage form in which it was administered.

The concept of biopharmaceutics

Many factors have been found to influence the time course of a drug in the plasma and hence at its site(s) of action. These include the foods eaten by the patient, the effect of the disease state on drug absorption, the age of the patient, the site(s) of absorption of the administered drug, the co-administration of other drugs, the physical and chemical properties of the administered drug, the type of dosage form, the composition and method of manufacture of the dosage form and the size of dose and frequency of administration of the dosage form. Thus, a given drug may exhibit differences in its bioavailability if it is administered in the same type of dosage form by different routes of administration, e.g. an aqueous solution of a given drug administered by the oral and intramuscular routes of administration. A given drug may also show differences in its bioavailability from one type of dosage form to another when given by the same route, e.g. a tablet, a hard gelatin capsule and an aqueous suspension administered by the peroral route. A given drug might show different bioavailabilities from different formulations of the same type of dosage form given by the same route of administration, e.g. different formulations of an aqueous suspension of a given drug administered by the peroral route. Variability in the bioavailability exhibited by a given drug from different formulations of the same type of dosage form or from different types of dosage froms etc., can cause patients to be under- or overmedicated. The result may be therapeutic failure or serious adverse effects particularly in the case of drugs which have a narrow therapeutic range (see Chapter 10).

The entry of a drug into the systemic circulation following the administration of a drug product usually involves

1 the release of the drug from its dosage form into solution in the biological fluids at the absorption site, and
2 the movement of the dissolved drug across biological membranes into the systemic circulation.

The study of the various factors which can affect these processes and the application of this knowledge to obtain the expected therapeutic effect from a drug product when it is used by a patient is known as *biopharmaceutics*.

BIBLIOGRAPHY

Cadwallader, D. E. (1973) *Biopharmaceutics and Drug Interactions*, F. Hoffman-La Roche, Basel.

Eadie, M. J., Tyrer, J. H. and Bochner, F. (1981) *Introduction to Clinical Pharmacology*, MTP Press Ltd, Lancaster.

Gibaldi, M. (1984) *Biopharmaceutics and Clinical Pharmacokinetics*, 3rd edn, Lea and Febiger, Philadelphia.

Notari, R. E. (1980) *Biopharmaceutics and Clinical Pharmacokinetics. An Introduction*, 3rd edn, Marcel Dekker Inc., New York.

Wagner, J. G. (1971) *Biopharmaceutics and Relevant Pharmacokinetics*, 1st edn, Drug Intelligence Publications, Hamilton, Illinois.

World Health Organisation (1974) *Bioavailability of Drugs: Principles and Problems*. Report of a WHO Scientific Group. Wld. Hlth. Org. Techn. Rep. Ser., 1974, No. 536. HMSO, London

Solutions

An understanding of the properties of solutions, the factors that affect solubility and the process of dissolution is essential because of the importance of solutions in so many areas of pharmaceutical formulation. It is recommended, therefore, that this chapter be read in conjunction with Chapters 3 and 5 for a full understanding of this topic.

A solution is an homogenous one-phase system consisting of two or more components. The solvent is that phase in which the dispersion occurs and the solute is that component which is dispersed as small molecules or ions in the solvent. In general the solvent is present in the greater amount but there are several exceptions. For example, Syrup BP contains 66.7% w/w of sucrose as the solute in 33.3% w/w of water as the solvent.

ADVANTAGES AND DISADVANTAGES OF SOLUTIONS AS AN ORAL DOSAGE FORM

Although tablets and capsules are more widely used than liquid preparations for oral administration the latter do exhibit several advantages.

1 Liquids are easier to swallow than solids and are therefore particularly acceptable for paediatric and geriatric use.

2 A drug must be in solution before it can be absorbed. A drug administered in the form of a solution is immediately available for absorption. Thus the therapeutic response is faster than if using a solid dosage form which must first disintegrate in order to allow the drug to dissolve in the gastrointestinal fluid before absorption can begin. Even if the drug should precipitate from solution in the acid conditions of the stomach it will be in a sufficiently wetted and finely divided state to allow rapid absorption to occur.
3 A solution is a homogenous system and therefore the drug will be uniformly distributed throughout the preparation. In suspension or emulsion formulations uneven dosage can occur due to phase separation on storage.
4 Some drugs, including aspirin and potassium chloride, can irritate and damage the gastric mucosa particularly if localized in one area as often occurs after the ingestion of a solid dosage form. Irritation is reduced by administration of a solution of a drug because of the immediate dilution by the gastric contents.

There are, however, several problems associated with the manufacture, transport, stability and administration of solutions.

1 Liquids are bulky and therefore inconvenient to transport and store. If breakage of the container should occur the whole of the product is immediately and irretrievably lost.
2 The stability of ingredients in aqueous solution is often poorer than if they were formulated as a tablet or capsule, particularly if they are susceptible to hydrolysis. The shelf life of a liquid dosage form is therefore often much shorter than the corresponding solid preparation. Not only is the stability of the drug of importance but also that of other excipients such as surfactants, preservatives, flavours and colours. The chemical stability of some ingredients can, however, be improved by the use of a mixed solvent system. The inclusion of a surfactant above its critical micelle concentration can also help because the hydrolytic degradation of a material may be reduced by its incorporation within the micelles (solubilization).
3 Solutions often provide suitable media for the growth of micro-organisms and may therefore require the incorporation of a preservative.
4 Accurate dosage usually depends on the ability of the patient to use a 5 ml spoon or, more rarely, a volumetric dropper.
5 The taste of a drug, which is usually unpleasant, is always more pronounced when in solution than when in a solid form. Solutions can, however, easily be sweetened and flavoured to make them more palatable.

FORMULATION OF SOLUTIONS

Aqueous solutions

Water is the most widely used solvent for use as a vehicle for pharmaceutical products because of its lack of toxicity, physiological compatibility and its ability to dissolve a wide range of materials.

For most preparations potable water can be used. This is water freshly drawn from the mains system and which is suitable for drinking. If this type is unobtainable then a suitable, though more expensive, alternative is Purified Water BP which has been freshly boiled and cooled before use to destroy any vegetative micro-organisms which may be present. Purified Water BP should be used, however, on all occasions where the presence of salts, often dissolved in potable water, is undesirable. Purified Water BP is normally prepared by the distillation or deionization of potable water.

Water for Injections BP must be used for the formulation of parenteral solutions and is obtained by the sterilization of pyrogen-free distilled water immediately after collection.

For the formulation of aqueous solutions of drugs, such as phenobarbitone sodium or aminophylline, which are sensitive to the presence of carbon dioxide or drugs which are liable to oxidation, such as apomorphine and ergotamine maleate, then Water for Injections BP free from carbon dioxide or free from air must be used. These are both obtained from apyrogenic distilled water in the same way as before, but are then boiled for at least 10 minutes, cooled, sealed in their containers whilst excluding air and then sterilized by autoclaving. For further details on parenteral solutions see Chapter 21.

Approaches to the improvement of aqueous solubility

Although water is very widely used for inclusion in pharmaceutical preparations, it may not be possible to ensure complete solution of all ingredients at all normal storage temperatures. Even if in solution it is important to ensure that the concentration of any material is not close to its limit of solubility as precipitation may occur if the product is cooled or if any evaporation of the vehicle should occur.

In these cases one or more of the following methods may be used in order to improve aqueous solubility.

Cosolvency

The solubility of a weak electrolyte or non-polar compound in water can often be improved by the addition of a water-miscible solvent in which the compound is also soluble. Vehicles used in combination to increase the solubility of a drug are called cosolvents (see Chapter 5) and often the solubility in this mixed system is greater than can be predicted from the material's solubility in each individual solvent.

Because it has been shown (Paruta *et al.*, 1964) that the solubility of a given drug is maximal at a particular dielectric constant of any solvent system, it is possible to eliminate solvent blends possessing other dielectric constants. In some cases, however, the actual solvent system used may be of greater importance (Gorman and Hall, 1964).

The choice of suitable cosolvents is somewhat limited for pharmaceutical use because of possible toxicity and irritancy, particularly if required for oral or parenteral use (Spiegal and Noseworthy, 1963). Ideally, suitable blends should possess values of dielectric constant between 25 and 80, although some oils are available with values of less than unity. The most widely used system which will cover this range is a water/ethanol blend, other suitable solvents including sorbitol, glycerol, propylene glycol and syrup. For example, a blend of propylene glycol and water is used to improve the solubility of co-trimoxazole, and paracetamol is formulated as an elixir by the use of alcohol, propylene glycol and syrup. For external application to the scalp betamethasone valerate is available dissolved in a water/isopropyl alcohol mixture.

For further details covering the suitability of different cosolvents see under their individual headings in this chapter.

pH control

If a drug is either a weak acid or a weak base then its solubility in water can be influenced by the pH of the system. A quantitative application of the Henderson–Hasselbalch equation (Chapter 3) will enable the solubility of such a material in water at a given pH to be determined, providing its pK_a and the solubility of its unionized species is known (see Chapter 3). The solubility of a weak base can be increased by lowering the pH of its solution whereas the solubility of a weak acid is improved by a pH increase. Some materials will accept or donate more than one hydrogen ion per molecule and will therefore possess more than one pK_a value and hence will exhibit a more complex solubility profile.

In controlling the solubility of a drug in this way it must be ensured that the chosen pH does not conflict with other product requirements. For example, the chemical stability of a drug may also depend on pH (Norton 1967; Smith, 1967) and in many cases the pH of optimum solubility does not coincide with the pH of optimum stability (Heward *et al.*, 1970). This may also be true for other ingredients especially dyes, preservatives and flavours.

The pH of solutions for parenteral and ophthalmic use, for application to mucous membranes or for use on abraded skin must also be controlled as extremes can cause pain and irritation (Lupton, 1942). This is particularly true for subcutaneous, intramuscular and c.n.s. injections because the solutions will not be rapidly diluted after administration.

In some instances the bioavailability of drugs may be influenced by the pH of their solution (Chapter 9) and changes in pH may also affect preservative activity by altering the degree of its ionization.

Often a compromise must be reached during formulation to ensure that the stability and solu-

bility of all ingredients, physiological compatibility and bioavailability are all adequate for the product's intended purpose.

The values of molar solubilities and dissociation constants of drugs which are reported in the literature or determined during preformulation studies are usually for the drug alone in distilled water. These values may differ in the final formulation due to the presence of other ingredients. For example, the inclusion of cosolvents such as alcohol or propylene glycol will lower the dielectric constant of the vehicle and therefore increase the solubility of the unionized form of the drug (Schumacher, 1969). This lowering of the polarity of the solvent system will also reduce the degree of dissociation of the drug and hence its pK_a will be increased. As this effect will increase the concentration of the unionized (less soluble) species an increase in the pH of the system may be necessary in order to maintain solubility. It must be realized, therefore, that maximum solubility may best be achieved by a judicious balance between pH control and concentration of cosolvent and can be determined as before by the application of the Henderson–Hasselbalch equation by substitution of the new values both for pK_a and for the molar solubilities of the unionized species.

Suitable buffer systems for the control of pH are discussed later in this chapter but care must be taken because the solubilities of sparingly soluble electrolytes can be decreased still further by the addition of a soluble electrolyte should they contain a common ion. The opposite can be true, however, if they do not possess common ions.

As solutions of non-electrolytes are not significantly affected by pH other methods of improving their solubility must be found.

Solubilization

The solubility of a drug which is normally insoluble or poorly soluble in water can often be improved by the addition of a surface-active agent. This phenomenon of micellar solubilization has been widely used for the formulation of solutions.

The amount of surfactant used for this purpose must be carefully controlled. A large excess is undesirable because of cost, possible toxic effects and its effect on product aeration during manufacture. Excessive amounts may also reduce the bioavailability of a drug due to its strong adsorption within the micelle. An insufficient amount of surfactant, however, may not solubilize all of the drug or may lead to precipitation on storage or on dilution of the product.

Reference to Fig. 6.13 will show that hydrophilic surfactants possessing HLB values above 15 will be of particular value as solubilizing agents. The material chosen must be non-toxic and non-irritant bearing in mind its intended route of administration. It must also be miscible with the solvent system, compatible with the other ingredients, free from disagreeable odour and taste and be non-volatile.

Examples include the solubilization of fat-soluble vitamins such as phytomenadione using polysorbates thus enabling their inclusion with water-soluble vitamins in the same formulation. The solubility of amiodarone hydrochloride can similarly be improved (Ravin *et al.*, 1969) although this drug can exhibit autosolubilization at high concentrations. The solubilization of iodine to produce iodophores is achieved by the use of macrogol ethers. These products exhibit several advantages over simple iodine solutions including an improved chemical stability, reduced loss of active agent due to sublimation, less corrosion of surgical instruments and, in some cases, enhanced activity. Many steroids are also poorly water soluble and alphadolone acetate and alphaxalone are together solubilized with polyoxyethylated castor oil to produce a solution suitable for intravenous administration as an anaesthetic. Other drugs which have been solubilized include antibiotics such as griseofulvin which has been formulated with cetamacrogol (Elworthy and Lipscomb, 1968). Polyoxyethylene/polyoxypropylene copolymers, some of which are also suitable for parenteral administration, are used to maintain the clarity of solutions for oral use. Lanolin derivatives have also been used for the solubilization of volatile and essential oils.

The solubility of phenolic compounds such as cresol and chloroxylenol which are normally soluble in water up to 2% and 0.03% respectively can be improved by solubilization with soaps. Lysol contains 50% cresol in an aqueous system

by the use of the potassium soaps of oleic, linoleic and linolenic acids. It may also be possible to combine the beneficial effects of solubilization and cosolvency in one formulation (Boon *et al.*, 1961). A 5% chloroxylenol solution can be formulated by the inclusion of potassium ricinoleate (which is formed *in situ* by the reaction between potassium hydroxide and castor oil), as well as ethanol and terpineol as cosolvents. Glycerol has also been used with polysorbate 80 to improve the solubility of vitamin A (Coles and Thomas, 1952).

For further details see Elworthy *et al.* (1968), Swarbrick (1965), Moore and Bell (1959), Monte-Bovi *et al.* (1954), Applewhite *et al.* (1954), Elworthy and Macfarlane (1965a, b).

To ensure that the optimum concentration of surfactant is chosen, a known weight or volume is added to each of a series of vials containing the solvent. Ensuring adequate temperature control, varying amounts of solubilizate are added to each vial in ascending order of concentration. The maximum concentration of drug which will form a clear solution with a given concentration of surfactant can be determined visually or by optical density measurement and is known as the maximum additive concentration (MAC). This method can be repeated for different amounts of surfactant to enable a graph to be constructed of MAC against surfactant concentration from which the optimum amount of solubilizing agent can be chosen for any required amount of drug (see Fig. 14.1). Alternatively, a ternary phase diagram can be constructed (see Fig. 14.2) which will present a more comprehensive picture of the effects of solubilizate, surfactant and solvent concentrations on the physical characteristics of the system.

The three axes form the three sides of an equilateral triangle each axis representing 0–100% of one of the components. Point A thus represents a formulation consisting of 50% solubilizate, 20% surfactant and 30% water. By plotting at each point a number representing one particular system (e.g. 1 = clear solution, 2 = emulsion etc.) and enclosing each system within a boundary, a phase diagram can be constructed. Suitable formulations which will give clear solutions will be immediately apparent and the best can then be chosen bearing in mind the desirable properties required for this type of product. It is also important to ensure that the formulation chosen does not lie too close to a phase boundary as the positions of these can depend on the storage temperature of the product. From this type of phase diagram the physical composition of diluted preparations can also be shown. Point B, for example, represents a product consisting of 40% solubilizate and 60% surfactant. The construction of a straight line from here to point C represents the dilution of the product with increasing concentrations of water. Should the concentration of drug to be included in the product be fixed then the third axis can be used to represent varying concentrations of a third excipient such as a cosolvent. These values must,

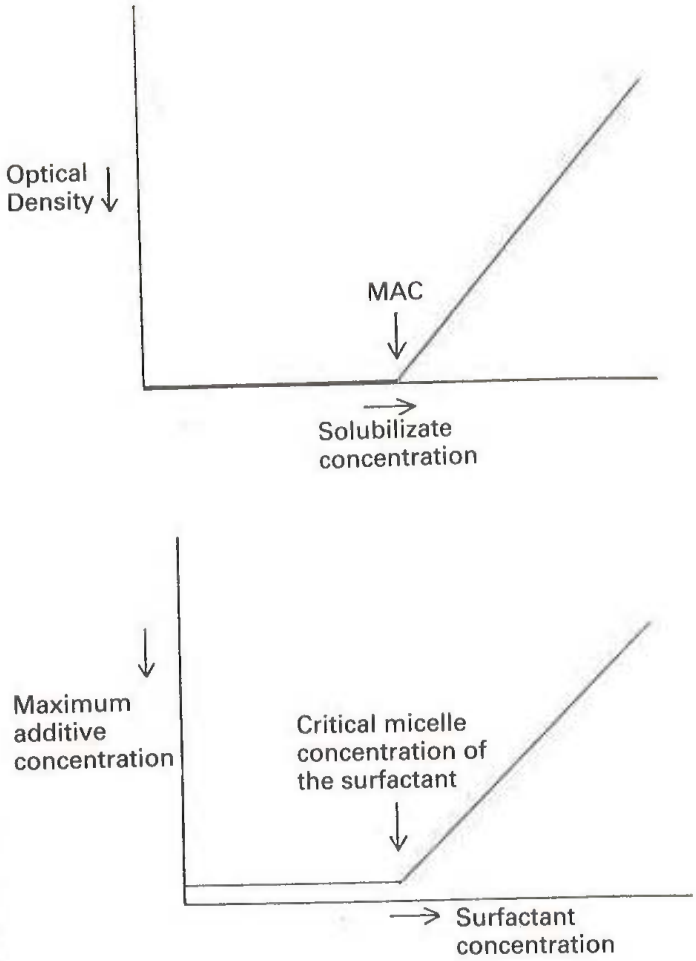


Fig. 14.1(a) Graph of optical density of a solubilizate/surfactant/solvent system versus solubilizate concentration at a fixed surfactant concentration showing the maximum additive concentration (MAC) (b) Determination of the MAC for a range of surfactant concentrations will thus provide this graph enabling the optimum concentration of surfactant to be chosen to solubilize a given amount of active material

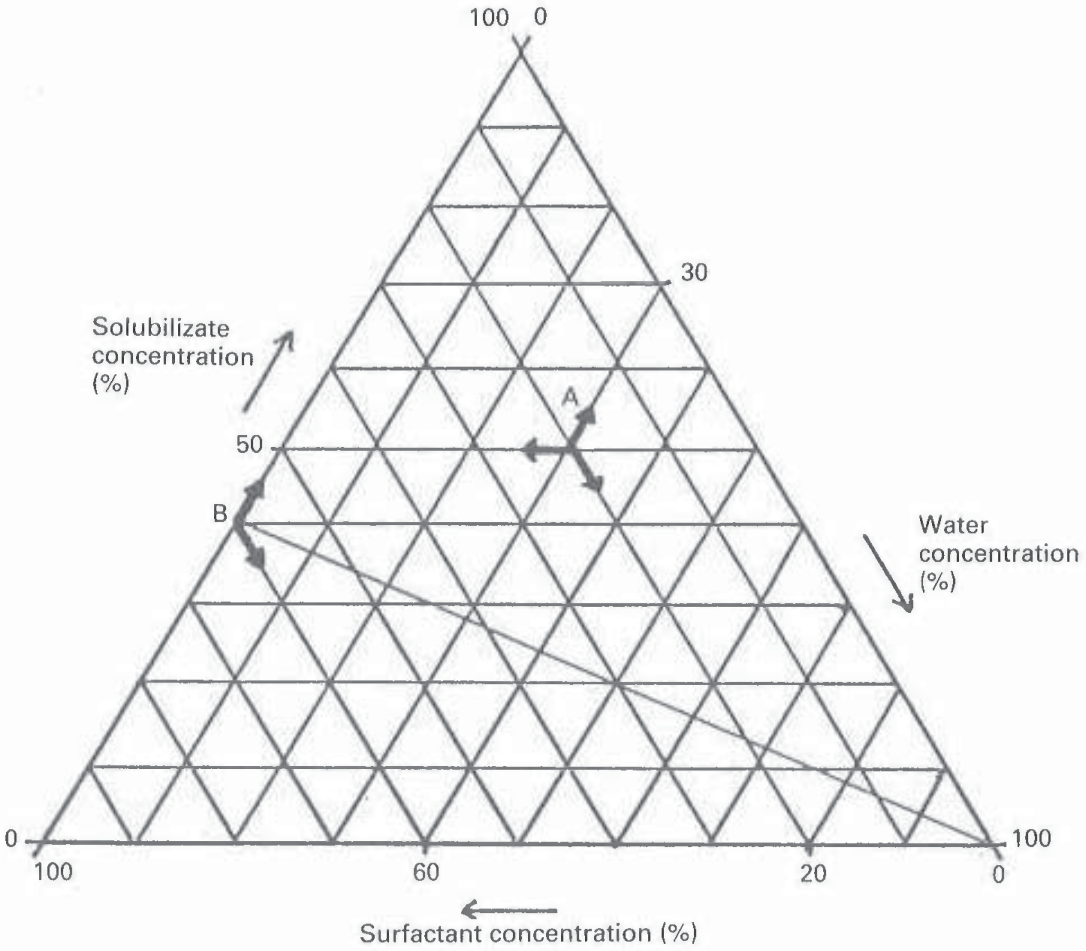


Fig. 14.2 Construction of a ternary phase diagram

however, be plotted as percentage drug plus excipient to ensure a maximum value of 100%.

Complexation

In some cases it may be possible to interact a poorly soluble drug with a soluble material to form a soluble intermolecular complex. As most complexes are macromolecular, however, they tend to be inactive, being unable to cross lipid membranes. It is essential, therefore, that complex formation is easily reversible so that the free drug is released during or before contact with biological fluids.

The term *hydrotropy*, which has been defined as the increase in aqueous solubility of a material by the inclusion of additives (Neuberg *et al.*, 1930), should be considered to be a form of complexation, although this definition also covers the increase in drug solubility which can sometimes be achieved by the inclusion of electrolytes.

It is not easy to predict if a drug will complex with a particular compound to give improved solubility. Many complexes are not water-soluble and may, in fact, be better suited for the prolonged release of the drug. Several well known examples are in general use, however, and include the complexation of iodine with a 10–15% solution of polyvinylpyrrolidone to improve the aqueous solubility of the active agent. Similarly the interaction of salicylates or benzoates with xanthines such as theophylline or caffeine or with carbazochrome is carried out for the same effect.

Chemical modification

As a last resort chemical modification of a drug may be necessary in order to produce a water-soluble derivative. Examples include the synthesis of the sodium phosphate salts of hydrocortisone, prednisolone and betamethasone. The water-soluble chloramphenicol sodium succinate has no

antibacterial activity of its own but is suitable for parenteral administration as a solution in order to obtain high blood levels after which it is converted back to the active base. Although many poorly soluble drugs have been modified in this way they are, of course, regarded as new chemical entities and thus full toxicity, pharmacology and preformulation studies may be required for these as well as for their parent compounds.

Particle size control

The size and shape of very small particles, if less than 1 μm diameter, can affect their solubility (May and Kolthoff, 1948). As particle size decreases solubility will increase. In practice, however, this phenomenon has little application in the formulation of solutions, but is of particular relevance in suspension formulation.

Non-aqueous solutions

The use of alternative solvents

If it is not possible to ensure complete solution of the ingredients at all storage temperatures or if the drug is unstable in aqueous systems it may be necessary to use an alternative solvent. The use of non-aqueous systems may also have other advantages. For example, the intramuscular injection of solutions of drugs in oils is often used for depot therapy and some drugs are specifically synthesized to improve their oil solubilities, the propionate and benzoate esters of testosterone and oestradiol, respectively, being good examples. The oily solution remains as a discrete entity within the muscle tissue, releasing the drug slowly into the surrounding tissue whereas a similar aqueous solution would diffuse readily and, being miscible with tissue fluid, would cause the drug to be released quickly.

It must be borne in mind that, in choosing a suitable solvent, its toxicity, irritancy and sensitizing potential must be taken into account as well as its flammability, cost, stability and compatibility with other excipients. It will be obvious that a greater choice of solvent will be available for inclusion into products for external application than those for internal use, while for parenteral products the choice is even further limited (Spiegal and Noseworthy, 1963).

A far wider range of solvents, however, is available for use during the manufacture of pharmaceutical products when the solvent is removed before packaging and therefore not present in the final product. Examples include acetone, light petroleum and chloroform although the latter is also used as a flavour and preservative in some extemporaneously prepared formulations.

The following is a classification of some of the most widely used non-aqueous solvents in pharmaceutical preparations.

Fixed oils of vegetable origin

These are non-volatile oils which consist mainly of fatty acid esters of glycerol. Almond oil, for example, which consists of glycerides mainly of oleic acid, is used as a solvent for Oily Phenol Injection BP, water being unsuitable because of the caustic nature of aqueous phenol solutions. Of similar chemical composition is arachis oil which is used as the solvent in Dimercaprol Injection BP. Olive oil, sesame oil, maize oil, cottonseed oil, soya oil and castor oil are all suitable for parenteral use, the latter also being used as the solvent in Physostigmine Oily Eye Drops BP and in some formulations of triamcinolone ear drops.

Ethyl oleate, which is a useful solvent for both Calciferol Injection BP and Testosterone Propionate Injections BP, is less viscous than the oils described above, and therefore more easily injected intramuscularly. Of similar viscosity is benzyl benzoate which can be used as an alternative solvent for dimercaprol.

Some fixed oils are sufficiently tasteless and odourless to be suitable for oral use as solvents for such materials as vitamins A and D. Fractionated coconut oil is used as the solvent for phenoxymethylpenicillin which would otherwise hydrolyse rapidly if present in an aqueous system. Veterinary formulations may also contain these solvents, arachis oil, for example, being used for hexachlorophane in the treatment of fascioliasis in ruminants.

Oils tend to be unpleasant to use externally,

however, unless presented as an emulsion. Arachis oil is one of the few examples and is used as the solvent in Methyl Salicylate Liniment BP.

Alcohols

Ethyl alcohol is the most widely used solvent in this class, particularly for external application, where its rapid evaporation after application to the skin imparts a cooling effect to such products as Salicyclic Acid Lotion BP. It is also particularly useful for the extraction of crude drugs being more selective than water. At concentrations greater than 15% it exhibits antimicrobial activity but because of its toxicity it is used orally or parenterally only at low concentrations, usually as a cosolvent with water. If required for external use then industrial methylated spirit (IMS), which is free from excise duty, is usually included rather than the more expensive ethanol. Because IMS contains 5% methyl alcohol as a denaturant it is rendered too toxic for internal use.

An alcohol possessing similar properties is isopropyl alcohol which is used externally as a solvent for dicophane. Its main advantage is that it is less likely to be abused than ethanol and denaturation is not necessary.

Polyhydric alcohols

Alcohols containing two hydroxyl groups per molecule are known as glycols but due to their toxicity are rarely used internally. One important exception to this is propylene glycol

$$CH_3.CH(OH)CH_2OH$$

which is often used in conjunction with water or glycerol as a cosolvent. It is used, for example, in the formulation of Digoxin Injection BP, Phenobarbitone Injection BP and some formulations of Diazepam Injection BP, Co-trimoxazole Intravenous Infusion BP and as the diluent for both Chloramphenicol Ear Drops BP and some brands of hydrocortisone ear drops and in many preparations for oral use.

The lower molecular weight polyethylene glycols (PEG) or macrogols have the general formula

$$OHCH_2(CH_2CH_2O)_nCH_2OH$$

PEG 400, for example, being used as a solvent in Erythromycin Ethylsuccinate Injection USP. They are also widely used as cosolvents with alcohol or water although their main use is in the formulation of water-miscible ointment bases.

There are also other glycols available, which, although rarely included in products for human use, can be used for extraction processes or as solvents in the formulation of veterinary and horticultural solutions. Examples include dipropylene glycol (the diluent in Piperonyl Butoxide Application BP Vet for veterinary use), diethylene glycol, ethylene glycol and their monoethyl ethers.

Glycerol, an alcohol possessing three hydroxyl groups per molecule, is also widely used particularly as a cosolvent with water for oral use. At higher concentrations it is used externally in, for example, Phenol Ear Drops BPC 1973.

Dimethylsulphoxide

This is a highly polar compound and is thought to aid the penetration of drugs through the skin. Although used mainly as a solvent in veterinary formulation, it is used as a carrier for idoxuridine, an antiviral agent, for application to human skin.

Ethyl ether

This material is widely used for the extraction of crude drugs but because of its own therapeutic activity is not used for the preparation of formulations for internal use. It is, however, used as a cosolvent with alcohol in some collodions.

Liquid paraffin

The oily nature of this material makes it unpleasant to use externally, although it is often used as a solvent for the topical application of drugs in emulsion formulations. At one time light liquid paraffin was widely used as the base for oily nasal drops which are now rarely used because of the possibility of causing lipoidal pneumonia if inhaled into the lungs. It has a minor use in veterinary formulation as a solvent in, for

example, anthelmintic drenches containing carbon tetrachloride.

Miscellaneous solvents

Isopropyl myristate and isopropyl palmitate are oily materials used as solvents for external use particularly in cosmetics where their low viscosity and lack of greasiness make them pleasant to use.

Dimethylformamide and dimethylacetamide have both been used as solvents in veterinary formulation but their toxicities render them unsuitable for human use. Kerosene too is also limited in its application being used mainly as a solvent for insecticides such as pyrethrum and piperonyl butoxide.

Xylene is present in some ear drops for human use to dissolve ear wax and glycofurol is a constituent of formulations of co-trimoxazole intramuscular injection.

As with aqueous systems it may be possible to improve the solubility of a drug in a particular vehicle by the addition of a cosolvent. For example, nitrocellulose is poorly soluble in both alcohol and ether but adequately soluble in a mixture of both. The formulation of Digoxin Injection BP, too, is best achieved by the inclusion of both ethyl alcohol and propylene glycol.

Formulation additives

Buffers

These are materials which, when dissolved in a solvent, will enable it to resist any change in pH should an acid or an alkali be added. The choice of suitable buffer depends on the pH and buffering capacity required. It must be compatible with other excipients and have a low toxicity.

Most pharmaceutically acceptable buffering systems are based on carbonates, citrates, gluconates, lactates, phosphates or tartrates. Borates can be used for external application but not to mucous membranes or to abraded skin (Windheuser, 1963).

As the pH of most body fluids is 7.4, products such as injections, eye drops and nasal drops should, in theory, be buffered at this value. Many body fluids themselves, however, have a buffering capacity and when formulating low volume intravenous injections or eye drops a wider pH range can be tolerated. This is potentially useful should a compromise be necessary between a pH which is physiologically acceptable and a pH of maximum stability and solubility and optimum bioavaibility. For further details on the use of buffers see Chapter 3.

Colours

Once a suitable flavour has been chosen it is often useful to include a colour which is associated with that flavour to improve the attractiveness of the product. Another reason for the inclusion of colours is to enable easy product identification particularly of poisonous materials including weedkillers or mineralized methylated spirit and, for example, to differentiate between the many types of antiseptic solution used in hospitals for the disinfection of skin, instruments, syringes etc. The development of a strongly coloured degradation product which does not affect the use of the product may occasionally be masked by the presence of a suitable colour.

It is essential to ensure, however, that any colour chosen is acceptable in the country in which the product is to be sold. A colour which is acceptable in one country may not be acceptable in another and as aspects of colour legislation can change quite frequently it is necessary to ensure that only the latest regulations are consulted. The legal departments of most dye manufacturers are usually willing to supply up to date information. The proliferation of nomenclature which exists for most colours can also cause confusion. For example, the water-soluble dye amaranth is also known as Bordeaux S, CI Food Red 9, and CI Acid Red 27. It has been allocated the Colour Index Number 16185 by the Society of Dyers and Colourists and the American Association of Textile Chemists and Colorists. Under the USA Food, Drug and Cosmetics Act it is known as FD and C Red Number 2 and a directive of the Council of European Communities has allocated it the reference number E 123.

As with flavours and perfumes there is available a range of both natural and synthetic colours. The former, which tend to be more widely acceptable,

can be classified into carotenoids, chlorophylls, anthocyanins and a miscellaneous group which includes riboflavines, caramel and extracts of red beetroot (Kläui, 1978). They can, however, exhibit the usual problems associated with natural products, namely variations in availability and in chemical composition, both of which may cause formulation difficulties.

Synthetic or 'coal tar' dyes tend to give brighter colours and are generally more stable than natural materials. Most of those which are suitable for pharmaceutical use are the sodium salts of sulphonic acids and therefore they may be incompatible with cationic drugs. Care must also be taken to ensure that any dye used is not adversely affected by pH or by u.v. radiation or by the inclusion of oxidizing or reducing agents (Swartz and Cooper, 1962) or surfactants (Scott *et al.*, 1960).

A useful review on the availability and use of colours can be found in *Martindale: The Extra Pharmacopoeia*.

Density modifiers

It is rarely necessary to control the density of a solution except when formulating spinal anaesthetics. Solutions of lower density than cerebrospinal fluid will tend to rise after injection and those of higher density will fall. Careful control both of the density of such injections and the position of the patient on the operating table will enable precise control of the area to be anaesthatized to be attained. The terms used to describe the density of injections in relation to that of spinal fluid are isobaric, hypobaric and hyperbaric, meaning of equal, lower and higher density respectively. The most widely used material for this type of density modification is dextrose.

Flavours and perfumes

The simple use of sweetening agents (q.v.) may not be sufficient to render palatable a product containing a drug with a particularly unpleasant taste. In many cases, therefore, a flavouring agent can be included. This is particularly useful in paediatric formulation to ensure patient compliance. The inclusion of flavours has the additional advantage of enabling identification of liquid products to be achieved easily.

Flavouring and perfuming agents can be obtained from either natural or synthetic sources. Natural products include fruit juices, aromatic oils such as peppermint and lemon oils, herbs and spices and distilled fractions of these. They are available as concentrated extracts, alcoholic or aqueous solutions, syrups or spirits and are particularly widely used in the manufacture of products for extemporaneous use. Artificial perfumes and flavours are of purely synthetic origin often having no natural counterpart. They tend to be cheaper, more readily available, less variable in chemical composition and more stable than natural products. They are usually available as alcoholic or aqueous solutions or as powders.

The choice of a suitable flavour can only be made as a result of subjective assessment and, as consumer preferences vary considerably, this task is not easy. Some guidance can, however, be given by reference to Table 14.1 which shows that certain flavours are particularly useful for the masking of one or more of the basic taste sensations of saltiness, bitterness, sweetness and sourness. These tastes are detected by sensory receptors on various areas of the tongue while the more subtle flavours are detected by the olfactory receptors.

Table 14.1

Taste of product	*Suitable masking flavour*
Salty	Apricot, butterscotch, liquorice, peach, vanilla
Bitter	Anise, chocolate, mint, passion fruit, wild cherry
Sweet	Vanilla, fruits, berries
Sour	Citrus fruits, liquorice, raspberry

In some cases there exists a strong association between the use of a product and its flavour or perfume content. For example, products intended for the relief of indigestion are often mint flavoured. This is because for many years mint has been used in such products for its carminative effect, but even in products containing other active agents, the odour and taste of mint are now firmly associated with antacid activity. Similarly the odour of terpineol is often associated with anti-

septic activity and in a competitive market it may therefore be unwise to alter these flavours or perfumes.

The fact that personal preferences for flavours and perfumes often vary with age can also aid the formulator. Children, in general, prefer fruity tastes and smells while adults choose flowery odours and acid flavours.

Other suitable materials for the masking of unpleasant tastes include menthol, peppermint oil and chloroform. In addition to their own particular tastes and odours they also act as desensitizing agents by the exertion of a mild anaesthetic effect on the sensory taste receptors. Flavour-enhancing agents such as citric acid for citrous fruits and glycine or monosodium glutamate for general use are now becoming more widely used.

Isotonicity modifiers

Solutions for injection, for application to mucous membranes and large volume solutions for ophthalmic use must be made iso-osmotic with tissue fluid to avoid pain and irritation. The relevance of osmotic pressure in the formulation of injections is discussed in Chapter 21.

If isotonicity is required it can only be accomplished after the addition of all other ingredients because of their effect on the osmotic pressure of a solution.

Preservatives

When choosing a suitable preservative it must be ensured that adsorption on to the container from the product does not occur or that its efficiency is not impaired by the pH of the solution or by interactions with other ingredients. For example, many of the widely used parahydroxybenzoic acid esters can be adsorbed into the micelles of some non-ionic surfactants (Barr and Tice, 1957) and, although their presence can be detected by chemical analysis, they are, in fact, unable to exert their antimicrobial activity. It is only by full microbiological challenge testing that the efficiency of a preservative system can be properly assessed.

Although most of the information concerning the preservation of emulsions and suspensions is also applicable to the formulation of solutions, a more comprehensive discussion on the preservation of pharmaceuticals can be found in Chapter 27.

Reducing agents and antioxidants

The decomposition of pharmaceutical products by oxidation can be controlled by the addition of reducing agents or antioxidants (see Chapter 13).

Sweetening agents

Low molecular weight carbohydrates and in particular sucrose are traditionally the most widely used sweetening agents. Sucrose has the advantage of being colourless, very soluble in water, stable over a pH range of about 4–8 and by increasing the viscosity of fluid preparations will impart to them a pleasant texture in the mouth. It will mask the tastes of both salty and bitter drugs and has a soothing effect on the membranes of the throat. For this reason sucrose, despite its cariogenic properties, is particularly useful as a vehicle for antitussive preparations. Polyhydric alcohols such as sorbitol, mannitol and to a lesser extent glycerol also possess sweetening power and can be included in preparations for diabetic use where sucrose is undesirable. Other less widely used bulk sweeteners include hydrogenated glucose syrup, isomalt, fructose and xylitol. Treacle, honey and liquorice are now very rarely used having only a minor application in some extemporaneously prepared formulations.

Artificial sweeteners can be used both in conjunction with sugars and alcohols to enhance the degree of sweetness or on their own in formulations for patients who must restrict their sugar intake. They are also termed intense sweeteners because, weight for weight, they are hundreds and even thousands of times sweeter than sucrose and are therefore rarely required at a concentration greater than about 0.2%. At present only four artificial sweeteners are permitted for oral use by the Food Additives and Contaminants Committee, the most widely used being the sodium or calcium salt of saccharin. They exhibit a high water solubility and are chemically and physically stable over a wide pH range. Less widely used are aspartame

(a compound of l-aspartic acid and l-phenylalanine, the use of which is increasing rapidly), acesulfame potassium and thaumatin (Parker, 1978). The main disadvantage of all artificial sweeteners is their tendency to impart a bitter or metallic after-taste and they are, therefore, often formulated with sugars to mask this (Brookes, 1965; Leach, 1970).

TYPES OF PREPARATIONS

Mixtures and draughts

Mixtures are usually aqueous preparations which can be in the form of either a solution or a suspension. Most preparations of this type are manufactured on a small scale as required and are allocated a shelf life of a few weeks before dispensing. Doses are usually given in multiples of 5 ml using a metric medicine spoon.

A draught is a mixture of which only one or two large doses of about 50 ml are given, although smaller doses are often necessary for children.

Elixirs

The terms mixture and elixir are often confused although an elixir refers strictly to a solution of a potent or nauseous drug. If the active agent is sensitive to moisture it may be formulated as a flavoured powder or granulation by the pharmaceutical industry and then simply dissolved in water immediately prior to administration. Dosage is usually given using a 5 ml medicine spoon although smaller volumes can be given using a volumetric dropper.

Linctuses

A linctus is a viscous preparation usually prescribed for the relief of cough. It usually consists of a simple solution of the active agent in a high concentration of sucrose often with other sweetening agents. This type of product, which is also designed to be administered in multiples of 5 ml, should be sipped slowly and not be diluted beforehand. The syrup content has a demulcent action on the mucous membranes of the throat. For diabetic use the sucrose is usually replaced by sorbitol and/or synthetic sweeteners.

Mouthwashes and gargles

Aqueous solutions for the prevention and treatment of mouth and throat infections can contain antiseptics, analgesics and/or astringents. They are usually diluted with warm water before use.

Nasal products

These are formulated as small volume solutions in an aqueous vehicle, oils being no longer used for nasal administration. Because the buffering capacity of nasal mucous is low, formulation at a pH of 6.8 is necessary. Nasal drops should also be made isotonic with nasal secretions using sodium chloride and viscosity can also be modified using cellulose derivatives if necessary. Active agents for administration by this route are usually for local use and include antibiotics, anti-inflammatories and decongestants.

Ear drops

These are simple solutions of drugs in either water, glycerol, propylene glycol or alcohol/water mixtures for local use and include antibiotics, antiseptics, cleansing solutions and wax softeners.

Enemas

Aqueous or oily solutions, as well as emulsions and suspensions, are available for the rectal administration of medicaments for cleansing, diagnostic or therapeutic reasons.

Preparations for external use

Lotions can be formulated as solutions and are designed to be applied to the skin without friction. They may contain either humectants, so that moisture is retained on the skin after application of the product, or alcohol which evaporates quickly, imparting a cooling effect and leaving the skin dry.

Liniments, however, are intended for massage

into the skin and can contain such ingredients as methyl salicylate or camphor as counter-irritants.

Liquids for application to the skin or mucous membranes in small amounts are often termed paints and are often applied with a small brush. The solvent is usually alcohol, acetone or ether which evaporates quickly leaving a film on the skin containing the active agent and a viscosity modifier such as glycerol to ensure prolonged contact with the skin.

Collodions are similar preparations which, after evaporation of the solvent, leave a tough, flexible film which will seal small cuts or hold a drug in intimate contact with the skin. The film former is usually pyroxylin (nitrocellulose) in an alcohol/ether or alcohol/acetone solvent blend. Often a plasticizer such as castor oil and an adherent like colophony resin are included.

Intermediate products

There are many pharmaceutical solutions which are designed for use during the manufacture of other preparations and which are rarely administered themselves. Aromatic waters, for example are aqueous solutions of volatile materials which are used mainly for their flavouring properties. Examples include peppermint water and anise water which also have carminative properties and chloroform water which also acts as a preservative. They are usually manufactured as concentrated waters and are then diluted, traditionally 1 to 40 in the final preparation.

Infusions, extracts and tinctures are terms used for concentrated solutions of active principles from animal or vegetable sources. Infusions are prepared by extracting the drug using 25% alcohol but without the application of heat. Traditionally these preparations are then diluted 1 to 10 in the final product. Extracts are similar products which are then concentrated by evaporation. Tinctures are alcoholic extracts of drugs but are relatively weak compared with extracts.

Spirits are also alcoholic solutions but of volatile materials which are mainly used as flavouring agents.

Syrups are concentrated solutions of sucrose or other sugars to which medicaments or flavourings are often added. For example Codeine Phosphate Syrup BPC 1973 is used as a cough suppressant and Orange Syrup BP contains dried bitter orange peel as a flavouring agent. Although syrups are used in the manufacture of other preparations, such as mixtures or elixirs, they can also be administered as products in their own right, the high concentrations of sugars imparting a sweetening effect.

As syrups can contain up to 85% of sugars, they are capable of resisting bacterial growth by virtue of their osmotic effect. Syrups containing lower concentrations of sugars often include sufficient of a polyhydric alcohol such as sorbitol, glycerol or propylene glycol in order to maintain a high osmotic gradient. Wild Cherry Syrup BP, for example, contains 80% sucrose with 5% glycerol. It is possible, however, in a closed container, for surface dilution of a syrup to take place. This occurs as a result of solvent evaporation which condenses on the upper internal surfaces of the container and then flows back on to the surface of the product thus producing a diluted layer which provides an ideal medium for the growth of certain micro-organisms. For this reason syrups often contain additional preservatives.

A further problem with the storage and use of syrups involves the crystallization of the sugar within the screw cap used to seal the containers thus preventing their release. This can be avoided by the addition of the polyhydric alcohols previously mentioned or by the inclusion of invert syrup which is a mixture of glucose and fructose.

STABILITY OF SOLUTIONS

Both the chemical and physical stability of solutions in their intended containers is important. A solution must retain its initial clarity, colour, odour, taste and viscosity over its allocated shelf life.

Clarity can easily be assessed by visual examination or by a measurement of its optical density after agitation. Colour too may be assessed both visually and spectrophotometrically and equipment suitable for the measurement of rheological properties of solutions has been covered earlier. The stability of flavours and perfumes is perhaps more difficult to assess. Although chromato-

graphic methods are used with varying success to quantify these properties, a considerable reliance must be placed on the organoleptic powers of a panel of assessors, who must be screened to ensure that their powers of olfaction and gustation are sufficiently sensitive. If a suitable majority of the panel members are unable to detect a difference between a stored sample and a freshly prepared reference material, it may be assumed that the taste or odour of the sample has not significantly changed.

MANUFACTURE OF SOLUTIONS

For both small and large scale manufacture of solutions the only equipment necessary is suitable mixing vessels, a means of agitation and a filtration system to ensure clarity of the final solution. During manufacture the solute is simply added to the solvent in a mixing vessel and stirring is continued until dissolution is complete. If the solute is more soluble at elevated temperatures it may be advantageous to apply heat to the vessel particularly if the dissolution rate is normally slow. Care must be taken, however, should any volatile or thermolabile materials be present. Size reduction of solid materials to increase their total surface areas should also speed up the process of solution.

Solutes present in low concentrations, particularly dyes, are often predissolved in a small volume of the solvent and then added to the bulk. Volatile materials such as flavours and perfumes are, where possible, added at the end of a process and after cooling if necessary, to reduce loss by evaporation. Finally it must be ensured that significant amounts of any of the materials are not irreversibly adsorbed on to the filtration medium used for final clarification. For discussion on suitable packaging materials and containers for solutions see Chapters 12 and 44.

REFERENCES

Barr, M. and Tice, L. F. (1957) The preservation of aqueous preparations containing nonionic surfactants. *J. Am. Pharm. Ass. (Sci. Edn)*, **46**, 445–451.

Boon, P. F. G., Coles, C. L. J. and Tait, M. (1961) The influence of the variations in solubilising properties of polysorbate 80 on the vitamin A palmitate: polysorbate 80:glycerol:water system. *J. Pharm. Pharmac.*, **13**, 200T–204T.

Brookes, L. G. (1956) The use of synthetic sweetening agents in pharmaceutical preparations and foods. *Chemist and Druggist*, **183**, 421–423.

Coles, C. L. J. and Thomas, D. F. W. (1952) The stability of vitamin A alcohol in aqueous and oily media. *J. Pharm. Pharmac.*, **4**, 898–903.

Elworthy, P. H. and Lipscomb, F. J. (1968) Solubilisation of griseofulvin by nonionic surfactants. *J. Pharm. Pharmac.*, **20**, 817–824.

Gorman, W. G. and Hall, G. D. (1964) Dielectric constant correlations with solubility and solubility parameters. *J.Pharm.Sci.*, **53**, 1017–1020.

Heward, M., Norton, D. A. and Rivers, S. M. (1970) Stability to heat and subsequent storage of chloramphenicol eye drops BPC. *Pharm. J.*, **204**, 386–387.

Kläui, H. (1978) the colouration of liquid galenical forms in fluid oral dosage forms. *Pharm.J.*, **222**, 92.

Leach, R. H. (1970) Factors limiting the use of sugars in paediatric formulations. *Pharm.J.*, **205**, 227–228.

Lupton, A. W. (1942) The pain effects of injections of varying pH. *Pharm.J.*, **148**, 105.

Martindale: The Extra Pharmacopoeia, 28th edn. (1982) Ed. J. E. F. Reynolds, The Pharmaceutical Press, London.

May, D. R. and Kolthoff, I. M. (1948) The aging of precipitates and coprecipitation XL. The solubility of lead chromate as a function of particle size. *J. Phys. Colloid Chem.*, 52, 836–854.

Neuberg, L. and Weinmann, F. (1930) Theory of hydrotropy. *Biochem. Z.*, **229**, 466–479.

Norton, D. A. (1967) Developments in the formulation and packaging of eye drops. *J. hosp. Pharm.*, **24**, 328–338.

Parker, K. J. (1978) Alternatives to sugar. The search for an ideal non-nutritive sweetener is almost a century old. *Nature*, **271**, 493–495.

Paruta, A. H., Sciarrone, B. J. and Lordi, N. G. (1964) Solubility of salicylic acid as a function of dielectric constant. *J.Pharm.Sci.*, **53**, 1349–1353.

Ravin, L. J., Shami, E. G., Intoccia, A., Rattie, E. and Joseph, G. (1969) Effect of polysorbate 80 on the solubility and 'in vitro' availability of 2-butyl-3-benzofuranyl 4-[2-(diethylamino)ethoxy]-3, 5-diiodophenyl ketone hydrochloride. (SKF 33134A). *J. Pharm. Sci.*, **58**, 1242–1245.

Schumacher, G. E. (1969) Some theoretical aspects of bulk compounding technology I. Ionic equilibria, pH and choice of solvents. *Am. J. hosp. Pharm.*, **26**, 354.

Scott, M. W., Goudie, A. J. and Huetteman, A. J. (1960) Accelerated color loss of certified dyes in the presence of nonionic surfactants. *J. Am. Pharm. Ass. (Sci. Edn)*, **49**, 467–472.

Smith, G. (1967) Eye drops. *Pharm. J.*, **198**, 53–61.

Spiegal, A. J. and Noseworthy, M. M. (1963) The use of nonaqueous solvents in parenteral products. *J. Pharm. Sci.*, **52**, 917–927.

Swartz, C. J. and Cooper, J. (1962) Colorants for

pharmaceuticals *J. Pharm. Sci.*, **51**, 89–95.
Windheuser, J. (1963) The effect of buffers on parenteral solutions. *Bull.Parent.Drug Ass.*, **17**, 1–8.

BIBLIOGRAPHY

Applewhite, R. W., Buckley, A. P. and Lewis Noble, W. (1954) Aqueous solutions of phenobarbital. *J. Am. Pharm. Ass. (Pract. Pharm. Edn.)*, **15**, 164–166.
Elworthy, P. H., Florence, A. T. and Macfarlane, C. B. (1968) *Solubilisation by Surface Active Agents*, Chapman and Hall, London.
Elworthy, P. H. and Macfarlane, C. B. (1965a) The physical chemistry of some nonionic detergents. *J. Pharm. Pharmac.*, **17**, 65–82.
Elworthy, P. H. and Macfarlane, C. B. (1965b) Further aspects of the physical chemistry of some nonionic detergents. *J. Pharm. Pharmac.*, **17**, 129–143.
Foster, A. (1979) Colour legislation and cosmetic and toiletries. *Int. J. cosmet. Sci.*, **1**, 221–245.
Monte-Bovi, A. J., Halpern, A. and Mazzola, P. (1954) Solubilising agents for elixirs. *J. Am. Pharm. Ass. (Pract. Pharm. Edn.)*, **15**, 162–164.
Moore, C. D. and Bell, M. (1959) Solubilisation. *Pharm. J.*, **182**, 171–173.
Swarbrick, J. (1965) Solubilised systems in pharmacy. *J. Pharm. Sci.*, **54**, 1229–1237.