1
Units

THE metric system has been a part of pharmaceutical practice for many years; indeed, as long ago as 1867, the first edition of the *British Pharmacopoeia* used metric quantities for volumetric analysis. This was extended in the 1898 edition to gravimetric analysis, and quantities for preparations were stated in parallel, using the metric and the Imperial systems. In the 1914 *Pharmacopoeia*, the quantities for preparations were expressed in metric only, although doses still used Imperial weights and measures, with an approximate metric equivalent. This continued until 1963, when doses were stated in the metric system only, so that all official standards became entirely metric. The metrication of pharmacy was completed on 1st March 1969, when all dispensing under the National Health Service was transferred to this system.

The use of metric weights and measures is, however, only part of a much greater change in which a rationalised system of metric units is coming into international use. Known as the *Système International d'Unités*, with *SI* as the accepted abbreviation, the objective is to derive almost all the quantities needed from a few base units, and to provide rules for the use of SI units to reduce errors and avoid ambiguities.

This book uses SI units, with recommended multiples and sub-multiples, and follows the recommendations of the International Organisation for Standardisation (ISO) and the British Standards Institution (BSI) with a few exceptions that are finding general acceptance where other permitted units are more convenient in practice than the recommended SI units.

In addition, it will be found that non-recommended units are used in certain cases where quotation is made from sources such as the *British Pharmacopoeia* which, at the time of writing, uses metric units, but does not yet follow SI recommendations.

The system of SI units has two important features:

1. All relationships are decimal.
2. It is a coherent system of units and in this respect it differs from metric systems previously in use. A coherent system is one in which the product or quotient of any two unit quantities is the unit of the resultant quantity. Thus, unit velocity results when unit length is divided by unit time, unit acceleration when unit velocity is divided by unit time, and unit force when unit mass is multiplied by unit acceleration. As well as providing straightforward relationships, this eliminates a number of special units and avoids former problems, such as the confusion between mass, force, and weight.

SI BASE UNITS

Six base units are used in the SI system (Table 1.1).

Table 1.1

Quantity	*Unit*	*Symbol*
length	metre	m
mass	kilogramme	kg
time	second	s
electric current	ampere	A
thermodynamic temperature	kelvin	K
luminous intensity	candela	cd

SUPPLEMENTARY SI UNITS

Certain additional supplementary units are used, including the radian (rad) for plane angles.

DERIVED SI UNITS

Further SI units are derived from the base units and are stated in terms of these units. Some of the derived units, which are used in this book and which have special names, are listed in Table 1.2. The remainder are included in the list of all symbols and units given in Table 1.4.

MULTIPLES AND SUB-MULTIPLES

As far as possible, numerical values should be kept between 0·1 and 1000, so that multiples and

Table 1.2
Derived SI Units with Special Names

Quantity	*Name of SI unit*	*Symbol*	*Expressed in terms of SI base units or derived units*
frequency	hertz	Hz	1 Hz = 1/s
force	newton	N	1 N = 1 kg m/s^2
work, energy, quantity of heat	joule	J	1 J = 1 N m
power	watt	W	1 W = 1 J/s

submultiples are recommended for use, based on the decimal range given in Table 1.3.

Thus, kilogramme represents 10^3 g and microgramme represents 10^{-6} g.

Table 1.3
Decimal Multiples and Sub-multiples

	Factor by which unit is multiplied	*Prefix*	*Symbol*
	10^{12}	tera	T
	10^9	giga	G
*	10^6	mega	M
*	10^3	kilo	k
	10^2	hecto	h
	10	deca	da
	10^{-1}	deci	d
	10^{-2}	centi	c
*	10^{-3}	milli	m
*	10^{-6}	micro	μ
	10^{-9}	nano	n
	10^{-12}	pico	p
	10^{-15}	femto	f
	10^{-18}	atto	a

To minimise the number of multiples and sub-multiples and to reduce the risk of error, only prefixes that represent 10 to a power that is a multiple of 3 are recommended. Those in use in this book are marked in Table 1.3 with an asterisk (*).

To avoid confusion, all calculations are performed in SI units themselves and not in decimal multiples or sub-multiples. In addition, only one prefix is applied to a unit at one time; for example, the term micrometre is used for one millionth of a metre, and not the term milli-millimetre.

EXCEPTIONS TO THE USE OF PREFERRED SI UNITS

Volume

The SI unit for volume is the cubic metre, with the cubic millimetre as the recommended sub-multiple. In practice, it is useful to have a unit of intermediate size and the litre is in common use. This name has been adopted as a synonym for the cubic decimetre and is used for general statement of volumes, with the millilitre as sub-multiple.

Pressure

The SI unit of force is the *newton*, defined as that force which when applied to a mass of 1 kilogramme gives it an acceleration of 1 metre per second per second. The newton per square metre is the SI unit for pressure, but for many purposes the unit is too small. For convenience, a unit known as the *bar* has been suggested, where 1 bar = 10^5 N/m^2. The advantage of the bar is that, for all practical purposes, 1 bar = 1 atmosphere pressure, so that pressures from 0 to 1 bar refer to pressures below atmospheric, while pressures from 1 bar upwards are above atmospheric. For high vacuum work, the unit N/m^2 is retained.

Temperature

The SI unit for temperature is the base unit of thermodynamic temperature, namely the kelvin (K), which is used in all calculations, and generally for physicochemical purposes.

As a 'customary' or practical unit, the degree Celsius (°C) is retained. This is identical to the former degree Centigrade, the change in name being due to the fact that the 'grade', and hence the 'centigrade', has another meaning in some countries.

The degree Celsius and the kelvin are identical units of temperature interval, but since 0°C = 273·15 K, then T°C = T + 273·15 K. It follows, therefore, that temperature intervals or temperature differences are the same in both cases, and these are stated in calculations as K. Hence, if water at 20°C is to be heated by a steam jacket at 100°C, the temperature difference is 80 K. To illustrate these various points:

The unit K is used in the Arrhenius equation, Eqn (6.35), which indicates the effect of temperature on the rate constant of a chemical reaction.

The coefficient of thermal conductivity is used in calculations in Chapter 12 and refers to a temperature interval, so that the units are W/mK.

The reference to the saturation temperature of steam at a pressure of two bars, made in Chapter 12,

Table 1.4

List of SI Units and Decimal Multiples and Sub-multiples

Quantity	*SI unit*	*Multiple or sub-multiple units*	*Other permitted units*
Part I: Space and time			
plane angle	rad (radian)		
length	m (metre)	mm μm	
area	m^2	mm^2	
volume	m^3	mm^3	litre and ml (1 litre = 1 dm^3)
time	s (second)	ks ms	minute, hour, day
velocity	m/s		
Part II: Periodic and related phenomena			
frequency	Hz (hertz)		
rotational frequency	1/s		
Part III: Mechanics			
mass	kg (kilogramme)	Mg g mg μg	
density (mass density)	kg/m^3		
force	N (newton)		
pressure	N/m^2	kN/m^2 MN/m^2	bar (1 bar = 10^5 N/m^2)
viscosity (dynamic)	$N\,s/m^2$		
kinematic viscosity	m^2/s		
surface tension	N/m		
energy, work	J (joule)	kJ	
power	W (watt)		
Part IV: Heat			
thermodynamic temperature	K (kelvin)		
Celsius temperature			[°C] (degree Celsius)
temperature interval	K		
heat, quantity of heat	J	kJ	
heat flow rate	W	kW	
density of heat flow rate	W/m^2		
thermal conductivity	W/mK		
coefficient of heat transfer	W/m^2K		
heat capacity	J/K	kJ/K	
specific energy	J/kg	kJ/kg	
specific latent heat	J/kg	kJ/kg	

is a customary temperature, so that it is given as 120·2°C.

Similarly, Chapter 24 gives data on equilibrium moisture contents for various materials at 20°C.

Amount of Substance (Symbol: n)

An additional unit, the mole, corresponding to the quantity 'amount of substance', has been recommended but it is not as yet approved by the international body concerned with the metric system.

The mole is the amount of substance that contains as many elementary units as there are atoms in 0·012 kg of carbon-12. The elementary unit must be specified and may be an atom, an ion, a molecule, etc. or a specified group of such species. For example—

1 mole of K_2SO_4 has a mass equal to 0·174 16 kg
1 mole of K^+ has a mass equal to 0·039 10 kg
1 mole of K_2^{++} has a mass equal to 0·078 20 kg
1 mole of SO_4^{--} has a mass equal to 0·095 96 kg
1 mole of $\frac{1}{2}SO_4^-$ has a mass equal to 0·047 88 kg

Units such as the gramme-molecule, gramme-equivalent, equivalent or gramme-ion will, therefore, become obsolete.

PRESENTATION OF NUMERICAL VALUES

In many countries, the comma is used as the decimal point, whereas it has been practice in the UK to use the comma to separate the digits of large numbers into groups of three.

To avoid confusion, this book follows present British practice whereby the decimal point is a full point placed above the line (·) and digits are separated by a small space between groups of three when five or more digits are used, except when data are expressed in tabular form; thus 1000 and 10 000.

BIBLIOGRAPHY

ANDERTON, P. and BIGG, P. M. (1967) *Changing to the Metric System.* London, H.M. Stationery Office.

British Standards Institution (1969) PD 5686, 1969 *The Use of SI Units.* London, The British Standards Institution.

MCGLASHAN, M. L. (1968) *Physico-chemical Quantities and Units.* London, Royal Institute of Chemistry.

2

Solutions

AN understanding of the properties of solutions, and the factors that affect solubility, is essential to pharmacists because of the importance of solutions in so many areas of pharmaceutical interest.

A true solution may be defined as a mixture of two or more components that form a homogeneous molecular dispersion; i.e. a system in which one component is dispersed as small molecules or ions throughout the other component. This definition differentiates true solutions from homogeneous colloidal dispersions, in which the particles of the dispersed component are larger than those in true solutions. (*See* Chapter 5 for a classification of disperse systems.)

In a solution composed of only two components (a binary system), that component which is dispersed throughout the other is termed the solute, and the component in which the dispersion occurs is termed the solvent. In general, the solvent is present in the greater amount, but several exceptions occur. For example, syrup contains about 65 per cent of sucrose in aqueous solution. In addition, it is often difficult to classify the components of mixtures of miscible liquids, such as alcohol and water, as solutes or solvents because either component may be regarded as the solvent depending on the composition of the mixture.

The Process of Dissolution

The transference of a molecule of a solute into solution in a solvent involves a change in the environments of both solute and solvent. The solute is separated from other similar molecules and becomes surrounded by solvent molecules. In addition, the solvent molecules are separated sufficiently from other similar molecules to create space for the accommodation of the solute molecule. Thus, dissolution will occur only if the solute and the solvent are mutually attracted to a degree that is sufficient to overcome the solute-solute and solvent-solvent intermolecular attractive forces.

Similar types of intermolecular force may contribute to solute-solvent, solute-solute, and solvent-solvent interactions. However, the strengths of these various contributing forces differ considerably. The Appendix shows that the attractive forces exerted between polar molecules are much stronger than those that exist between polar and non-polar molecules or between non-polar molecules themselves.

Thus, in a polar solute, where the intermolecular interaction is appreciable, transference of solute molecules into solution will occur only if the solute-solvent association is even stronger. Such strong solute-solvent interaction will result only if the solvent is also a polar substance (e.g. water), since a non-polar solvent (e.g. benzene) will be unable to exert sufficient attraction on a molecule to cause it to separate from other solute molecules.

Conversely, the dissolution of a non-polar substance such as paraffin wax, the intermolecular attractions of which are relatively weak, will occur only if the solute-solvent interaction is stronger than the solvent-solvent interaction. A marked intermolecular association between solvent molecules, such as that which exists between the molecules of a polar solvent (e.g. water) will therefore tend to prevent dissolution of a non-polar solute, so that solvents for this type of solute tend to be restricted to non-polar liquids (e.g. benzene).

The above considerations are often expressed in the very general manner that 'like dissolves like'; i.e. a polar substance will dissolve in a polar solvent and a non-polar substance will dissolve in a non-polar solvent. However, such a generalisation should be treated with caution, since the intermolecular attractions involved in the process of dissolution are influenced by factors that are not obvious from a consideration of the overall polarity of a molecule. For example, the possibility of hydrogen-bond formation (*see* Appendix) between solute and solvent may be more significant than polarity.

Methods of Expressing the Concentration of Solutions

It is assumed that the student is familiar with concentration terms such as normality and molarity.

Although such expressions are included in many existing reference books for pharmacists, the introduction of the SI system of units has either made them obsolete or will eventually lead to their abandonment.

The methods recommended by McGlashan (1968) for expressing the amount of substance in a given solution include—

(*a*) the molality of solute, which is defined as the number of moles of solute divided by the mass of the solvent, and its SI units are mole kg^{-1}. (The term molality was used in the cgs scale and, although the name is likely to be retained as the name of an SI quantity, the use of the abbreviation 'molal' is not recognised as a unit symbol by the General Conference on Weights and Measures, and the abbreviation 'm' for molality is to be discouraged because this letter is used as a symbol for metre.)

(*b*) the concentration of solute, which is defined as the number of moles of solute divided by the volume of the solution, and its SI units are mole m^{-3}.

In addition, it is also possible to express concentration of a solution in terms of the mass or volume of a solute contained in a given mass or volume of solution. It should be remembered that the basic SI units for mass and volume are the kilogramme and cubic metre, respectively. These units may be unwieldy in certain instances, and appropriate prefixes to indicate decimal fractions or multiples should therefore be used. The previous use of the litre as a common unit of volume will probably lead to the use of the cubic decimetre (dm^3) as a common unit of volume. It is unfortunate that the term kilogramme and its symbol kg suggest a multiple of a basic unit, and make difficult construction of decimal fractions of this unit by the addition of prefixes. A new name and symbol will probably be introduced in the future.

PERCENTAGE EXPRESSIONS

The concentration of a solution may be expressed as a percentage; i.e.

$$\text{concentration} = \frac{\text{mass or volume of solute}}{\text{mass or volume of solution}} \times 100$$

Percentage weight in volume (% w/v), percentage weight in weight (% w/w), percentage volume in weight (% v/w) and percentage volume in volume (% v/v) are often used in pharmaceutical practice. For example, the strengths of Pharmacopoeial preparations may be defined as percentages; e.g. Belladonna Tincture (BP 1968) contains 0·03 % w/v of the alkaloids of Belladonna Herb.

Solubility

The solubility of a substance in a solvent at a given temperature and pressure, is the amount of substance that has passed into solution when equilibrium is attained between the solution and excess, i.e. undissolved, substance. The solution that is obtained under these conditions is termed a saturated solution. It is possible to obtain solutions that are supersaturated. However, they are unstable, and scratching the side of the container, the presence of dust, or the addition of undissolved solute will provide nuclei that readily lead to precipitation of the excess solute.

METHODS OF EXPRESSING SOLUBILITY

Solubilities may be expressed quantitatively by the same methods as are used for stating concentration. The *British Pharmacopoeia* (1968) expresses solubilities as the number of parts by volume of solvent required to dissolve one part by weight of a solid or one part by volume of a liquid. Unless otherwise specified, these solubilities apply at room temperature. Figures given under the side heading 'Solubility in the Pharmacopoeial monographs, are only approximate and are not intended to be official requirements. However, statements under side headings such as 'Solubility in Alcohol' are exact and are intended as part of the official requirements for that substance.

TYPES OF SOLUTION

Solutions may be classified on the basis of the physical states of the components. Since there are three states of matter, i.e. solid, liquid, and gas, nine different types of solution with two components are possible, as shown in Table 2.1.

Solutions of solids in liquids are the most important in pharmacy, and only this type of system is

Table 2.1
Types of Solution

Solute	*Solvent*
Gas	Gas
Liquid	Gas
Solid	Gas
Gas	Liquid
Liquid	Liquid
Solid	Liquid
Gas	Solid
Liquid	Solid
Solid	Solid

discussed in the present chapter. Further information on most of the systems shown in Table 2.1 that are involved in pharmaceutical processes or products is given in the following chapter.

DETERMINATION OF THE SOLUBILITY OF SOLIDS IN LIQUIDS

The following points should be observed in all solubility determinations.

(*a*) The solvent and solute must be pure.
(*b*) A saturated solution must be obtained before any solution is removed for analysis.
(*c*) The method of separating a sample of saturated solution from undissolved solute must be satisfactory.
(*d*) The method of analysing the solution must be reliable.
(*e*) Temperature must be adequately controlled.

A saturated solution is obtained either by stirring excess powdered solute with solvent for several hours at the required temperature until equilibrium has been attained, or by warming the solvent with an excess of the solute and allowing the mixture to cool to the required temperature. It is essential that some undissolved solid should be present at the completion of this stage in order to ensure that the solution is saturated.

A sample of the saturated solution is obtained for analysis by separating the solution from the undissolved solid. Filtration is usually used, but precautions should be taken to ensure that: (*a*) it is carried out at the temperature of the solubility determination, in order to prevent any change in the equilibrium between dissolved and undissolved solute; and (*b*) loss of a volatile component does not occur.

Different methods of analysis may be applied to the saturated solution depending on the type of system involved. For example, if one of the components is volatile and one is non-volatile, the amount of the latter can be determined by heating to constant weight. Alternatively, the solute may be converted to an insoluble compound by chemical reaction, and the weight of this may be obtained after filtration and drying. Volumetric analysis may be used, especially for those compounds that exhibit the reactions of acids, alkalis, chlorides, etc. which are readily determined by this means. Physical measurements offer a further means of analysis. For example, electrical conductivity measurements are suitable for sparingly soluble electrolytes, optical rotation may be used for optically active compounds, or a radioactive indicator method may be employed. This latter method involves the preparation of the test material in such a way that it contains a known proportion of a radioactive indicator. A saturated solution is made and its level of radioactivity may be used to determine the concentration of solute.

FACTORS AFFECTING THE SOLUBILITY OF SOLIDS IN LIQUIDS

1. *Temperature*

In most cases the dissolution of a solid in a liquid involves the absorption of heat; i.e. it is an endothermic process with a positive heat of solution. If this type of system is heated, it will tend to react in a way that will nullify the constraint imposed upon it; i.e. the rise in temperature. This tendency is an example of Le Chatelier's principle. Thus, a rise in temperature will lead to an increase in the solubility of a solid with a positive heat of solution. Conversely, if the dissolution of a solid involves the liberation of heat; i.e. it is an exothermic process with a negative heat of solution, then an increase in temperature will lead to a decrease in the solubility.

Solubility curves are often used to indicate the effect of temperature on the solubility of a given substance. Some of these are shown in Fig. 2.1. It can be seen that potassium nitrate shows a marked increase in solubility with rise in temperature, while calcium acetate shows a small decrease. These

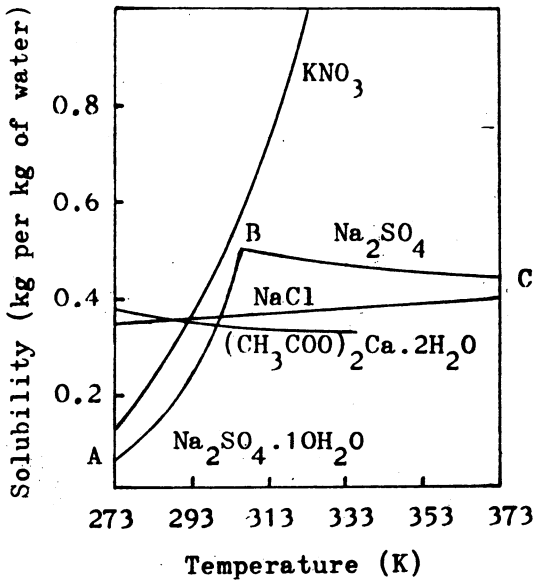


Fig. 2.1 Solubility curves for various substances in water

compounds are therefore examples of substances with positive and negative heats of solution, respectively. The dissolution of sodium chloride involves little absorption of heat, as indicated by the approximately horizontal solubility curve for this compound.

The majority of solubility curves are continuous curves, but abrupt changes in slope may sometimes be observed if the nature of the solid phase in contact with the solution alters. For example, sodium sulphate exists as the decahydrate $Na_2SO_4.10\,H_2O$ up to a temperature of 305·55 K, and its dissolution in water is an endothermic process. Above this temperature the solid is converted into the anhydrous form, Na_2SO_4, and the dissolution of this compound is an exothermic process. The solubility curve therefore exhibits a break at 305·55 K, which is known as a transition point, and *AB* and *BC* in Fig. 2.1 represent the solubility curves for the decahydrate and the anhydrous form of sodium sulphate, respectively.

2. *Particle Size of the Solid*

The changes in interfacial free energy (*see* p. 33) that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size, as indicated by Eqn (2.1),

$$\log \frac{s}{s_0} = \frac{2\gamma M}{2{\cdot}303RT\rho r} \qquad (2.1)$$

where s is the solubility of small particles of radius r,
s_0 is the normal solubility (i.e. of a solid consisting of fairly large particles),
γ is the interfacial energy (*see* Chapter 4),
M is the molecular weight of the solid,
ρ is the density of the bulk solid,
R is the gas constant, and
T is the thermodynamic temperature.

This effect may be significant in the storage of pharmaceutical suspensions, since the smaller particles in such a suspension will be more soluble than the larger ones. As the small particles disappear, the overall solubility of the suspended drug will decrease, and growth of the larger particles will occur. The occurrence of crystal growth by this mechanism is of particular importance in the storage of suspensions intended for injection (Gunn and Carter, 1965).

The increase in solubility with decrease in particle size ceases when the particles have a very small radius, and any further decrease in size causes a decrease in solubility. It has been postulated that this change arises from the presence of an electrical charge on the particles and that the effect of this charge becomes more important as the size of the particles decreases (Buckley, 1951).

3. *Solvent*

It will be appreciated from the discussion of the mechanism of solution that the solubility of a solid depends on the nature of the solvent. The solubilities of a particular solid in a variety of liquids will, therefore, differ. In addition, changes in the properties of a solvent caused by the addition of other substances, may affect the solubility of a solid in the system (p. 12).

Water is the most common solvent encountered in pharmaceutical practice, especially for preparations intended for internal use. Ethanol, usually in various mixtures with water, is also popular. Simple organic liquids such as ether, chloroform, acetone, and various glycols and oils, may be used in addition to water and alcohol in preparations intended for external use. (*See* Gunn and Carter, 1965, for solvents used in parenteral products.)

4. *pH*

Many drugs behave as weak acids or bases and their solubility is therefore affected by the pH of an aqueous solvent. For example, a weakly acidic drug such as acetylsalicylic acid (aspirin) will be more soluble in alkaline solution, since it will be converted to the more soluble salt. Conversely, the drug will be precipitated from aqueous solution if the pH is lowered by the addition of a strong acid Similarly, a weakly basic drug will be more soluble in solutions of low pH and will precipitate if the pH is raised by the addition of an alkali.

5. *Additional Substances*

(*a*) *Common Ion Effect.* The solubility of a sparingly soluble electrolyte is decreased by the addition of a second electrolyte that possesses a similar ion to the first. This is known as the common ion effect.

In a saturated solution in contact with undissolved solid, the equilibrium may be represented as follows for a compound *AB*:

$$\underset{\text{undissolved solid}}{AB_{(s)}} \rightleftharpoons \underbrace{\underset{\text{undissociated molecule}}{AB} \rightleftharpoons \underset{\text{ions}}{A^+ + B^-}}_{\text{species in solution}}$$

If the salt is sparingly soluble, then the concentration of solute is sufficiently small to assume complete dissociation into ions. The overall equilibrium may then be represented by

$$AB_{(s)} \rightleftharpoons A^+ + B^- \qquad (2.2)$$

From the Law of Mass Action, the equilibrium constant (K) for this reversible reaction is given by

$$K = \frac{[A^+][B^-]}{[AB]_{(s)}}$$

where the square brackets indicate concentration of the respective components. Furthermore, the concentration of a solid may be regarded as being constant

$$\therefore \quad K = \frac{[A^+][B^-]}{\text{constant}}$$

$$\therefore \quad K_s' = [A^+][B^-] \qquad (2.3)$$

where K_s' is a constant and is known as the solubility product of compound AB.

If each molecule of the salt contains more than one ion of each type, e.g. A_xB_y, then in the definition of the solubility product the concentration of each ion is expressed to the appropriate power; i.e.

$$K_s' = [A^+]^x[B^-]^y$$

These equations for the solubility product are only applicable to solutions of sparingly soluble salts.

If K_s' is exceeded by the product of the concentration of the ions, i.e. $[A^+][B^-]$, then the equilibrium shown above, Eqn (2.2), moves towards the left in order to restore the equilibrium, and solid AB is precipitated. The product $[A^+][B^-]$ will be increased by the addition of more A^+ ions produced by the dissociation of another compound, e.g. $AX \rightarrow A^+ + X^-$, where A^+ is the common ion. Solid AB will be precipitated and the solubility of this compound is therefore decreased. This is known as the common ion effect. The addition of common B^- ions would have the same effect.

The precipitating effect of common ions is, in fact, less than that predicted from Eqn (2.3). The reason for this is explained in the following section.

(*b*) *Effect of Indifferent Electrolytes.* The solubility of a sparingly soluble electrolyte may be increased by the addition of a second electrolyte that does not possess ions common to the first; i.e. an indifferent electrolyte.

The definition of the solubility product of a sparingly soluble electrolyte in terms of the concentration of ions produced at equilibrium, as indicated by Eqn (2.3), is only an approximation from the more exact thermodynamic relationship expressed by Eqn (2.4),

$$K_s = a_{A^+} \cdot a_{B^-} \qquad (2.4)$$

where K_s is the solubility product of compound AB and a_{A^+} and a_{B^-} are known as the activities of the respective ions. The activity of a particular ion may be regarded as its 'effective concentration'. In general, this has a lower value than the actual concentration, because some ions produced by dissociation of the electrolyte are strongly associated with oppositely charged ions and do not contribute so effectively as completely unassociated ions to the properties of the system. At infinite dilution, the wide separation of ions prevents any interionic association, and the molar concentration (c_{A^+}) and activity (a_{A^+}) of a given ion (A^+) are then equal; i.e.

$$a_{A^+} = c_{A^+}, \quad \text{or} \quad \frac{a_{A^+}}{c_{A^+}} = 1$$

As the concentration increases, the effects of interionic association are no longer negligible, and the ratio of activity to molar concentration becomes less than unity; i.e.

$$\frac{a_{A^+}}{c_{A^+}} = f_{A^+}$$

or

$$a_{A^+} = c_{A^+} \cdot f_{A^+}$$

where f_{A^+} is known as the activity coefficient of A^+. If concentrations and activity coefficients are used instead of activities in Eqn (2.4) then

$$K_s = (c_{A^+} \cdot c_{B^-})(f_{A^+} \cdot f_{B^-})$$

The product of the concentrations, i.e. $(c_{A^+} \cdot c_{B^-})$, will be a constant (K_s') as shown by Eqn (2.3), and $(f_{A^+} \cdot f_{B^-})$ may be equated to $f^2_{A^+B^-}$, where $f_{A^+B^-}$ is the mean activity coefficient of the salt AB, i.e.

$$K_s = K_s' f^2_{A^+B^-} \qquad (2.5)$$

Since $f_{A^+B^-}$ varies with the overall concentration of ions present in solution (the ionic strength), and since K_s is a constant, it follows that K_s' must also vary with the ionic strength of the solution in an inverse manner to the variation of $f_{A^+B^-}$. Thus, in a system containing a sparingly soluble electrolyte without a common ion, the ionic strength will have an appreciable value and the mean activity coefficient $f_{A^+B^-}$ will be less than one.

From Eqn (2.5) it will be seen that K_s' will, therefore, be greater than K_s. In fact, the concentration solubility product K_s' will become larger and larger as the ionic strength of the solution increases. The solubility of AB will therefore increase as the concentration of added electrolyte increases.

This argument also accounts for the fact that if no allowance is made for the variation in activity with ionic strength of the medium, the precipitating effect of common ions is less than that predicted from the Law of Mass Action.

(*c*) *Effect of Non-electrolytes on the Solubility of Electrolytes.* The solubility of electrolytes depends on the dissociation of dissolved molecules into ions. The ease of this dissociation is affected by the dielectric constant of the solvent, which is a measure of the polar nature of the solvent. Liquids with a high dielectric constant (e.g. water and formic acid) are able to reduce the attractive forces that operate between oppositely charged ions produced by dissociation of an electrolyte.

If a water-soluble non-electrolyte such as alcohol is added to an aqueous solution of a sparingly soluble electrolyte, the solubility of the latter is decreased because the alcohol lowers the dielectric constant of the solvent and ionic dissociation of the electrolyte becomes more difficult

(*d*) *Effect of Electrolytes on the Solubility of Non-electrolytes.* Non-electrolytes do not dissociate into ions in aqueous solution, and in dilute solution the dissolved species therefore consists of single molecules. Their solubility in water depends on the formation of weak intermolecular bonds (hydrogen bonds) between their molecules and those of water. The presence of a very soluble electrolyte (e.g. ammonium sulphate), the ions of which have a marked affinity for water, will reduce the solubility of a non-electrolyte by competing for the aqueous solvent and breaking the intermolecular bonds between the non-electrolyte and water. This effect is important in the precipitation of proteins (p. 60).

(*e*) *Effect of Complex Formation.* The apparent solubility of a solute in a particular liquid may be increased or decreased by the addition of a third substance which forms an intermolecular complex with the solute. The solubility of the complex will determine the apparent change in the solubility of the original solute. For example, the formation of the complexes between 3-aminobenzoic acid and various dicarboxylic acids has been shown to increase the apparent water solubility of the former compound (Wurster and Kilsig, 1965), and Kostenbauder and Higuchi (1956) have shown that soluble and insoluble complexes may be obtained by interactions between various amides and 4-hydroxybenzoic acid, salicylic acid, chloramphenicol, and phenol. Use is also made of complex formation as an aid to solubility in the preparation of solution of mercuric iodide (HgI_2). The latter is not very soluble in water but it is soluble in aqueous solutions of potassium iodide because of the formation of a water-soluble complex, $K_2(HgI_4)$.

(*f*) *Effect of Surface Active Agents.* These compounds are capable of forming large aggregates at certain concentrations in aqueous solutions. Organic compounds with low water solubilities are taken into the interior of these aggregates, and the apparent water solubilities of the organic compounds are increased. The phenomenon is termed solubilisation, and more information is given in Chapter 5.

Dissolution Rates

The dissolution of a solid in a liquid involves the transfer of mass from a solid to a liquid phase. The overall transfer process may be regarded as being composed of two consecutive stages. The first of these, which is an interfacial reaction that results in the liberation of solute molecules from the solid phase, is followed by the transport of solute away from the interfacial boundary under the influence of diffusion or convection. Like any complex reaction that involves consecutive stages, the overall rate of mass transfer in dissolution will be determined by the rate of the slowest stage. If the rates of the two consecutive stages are comparable in magnitude, then both stages will influence the overall rate of transfer.

The Noyes-Whitney Eqn (2.6) indicates that the rate of dissolution (dc/dt) is proportional to the surface area, S, of the solid and the concentration gradient ($C_s - C$), where C_s is the concentration of the substance in a thin saturated liquid film (boundary layer) adjacent to the solid surface, and C is the concentration in the surrounding bulk medium. K is a proportionality constant that is known as the dissolution rate constant.

$$\frac{dc}{dt} = KS(C_s - C) \qquad (2.6)$$

This equation assumes that the rate of mass transfer depends on the rate at which the solute diffuses from the thin boundary layer into the bulk solution. Therefore, K will depend on the diffusion coefficient of the solute and the thickness of the diffusion pathway, and it will be influenced by factors that influence the diffusion coefficient and the film thickness.

FACTORS THAT AFFECT DISSOLUTION RATES

1. *Factors Affecting the Complete System*

(*a*) *Temperature.* It has been shown previously that Le Chatelier's principle will apply to the process of dissolution. An increase in temperature will increase the solubility of a solid with a positive heat of solution. The solid will therefore dissolve at a more rapid rate on heating the system. When complete

dissolution has been achieved the system can be cooled to the required temperature, and the substance will remain in solution provided its maximum solubility at the lower temperature is not exceeded. Care should be taken when using this means of increasing the rate of dissolution to ensure that precipitation of the solute does not occur on cooling.

Conversely, a decrease in temperature may be used to increase the dissolution rate of a substance with a negative heat of solution; e.g. paraldehyde.

(*b*) *Agitation.* The rate of transfer of solute from the boundary layer to the surrounding solute will depend on the concentration gradient between these two regions, as indicated by Eqn (2.6), and on the thickness of the diffusion pathway. This latter factor is included in the value of K in Eqn (2.6). Agitation will help to increase a dissolution rate by reducing the thickness of the diffusion pathway and by bringing fresh solvent into contact with the boundary layer, so producing a high value for $(C_s - C)$. The rate of dissolution may therefore be markedly affected by agitation or stirring, and particular care should be paid to this factor in the measurement of these rates. However, it should be borne in mind that the overall rate of mass transfer by dissolution will be independent of agitation if the interfacial reaction that involves the liberation of molecules from the solid phase into the solution is the rate determining stage.

An increase in dissolution rate may also be achieved by proper positioning of the solid in order to take advantage of the difference in densities of the solution and solvent. A solution is usually denser than its solvent, so that if the solid is supported by some means in the upper part of the liquid the denser solution will fall and be replaced by fresh solvent. This process is less efficient than continuous stirring but it is made use of in the extraction of soluble materials from crude drugs.

2. *Changes in the Characteristics of the Solid*

(*a*) *Surface Area.* The Noyes-Whitney Eqn (2.6) shows that the dissolution rate is increased by an increase in the surface area of the solid. Reduction in particle size is effective in creating an increase in surface area, as indicated by Eqn (2.7)—

$$S = \frac{6m}{d\rho} \qquad (2.7)$$

where, d is the mean diameter of the particles, m is the mass of the particles, and ρ is the density of the particles. If a unit mass of powder with a density of 1 is considered, then

$$S = \frac{6}{d}$$

and a ten-fold reduction in the mean particle diameter will provide a similar increase in the surface area.

The porosity of the solid particles will also influence the area of contact between the solid and liquid phases. The rate of dissolution of material from the solid surfaces inside pores is less than that from a plane surface because the pathway for diffusion is longer in the former case. The effect of porosity ceases to be of importance when the pores are of molecular dimensions and become too small to allow access of solvent molecules.

(*b*) *Polymorphism.* A substance is said to exhibit polymorphism if it can exist in more than one type of structure, which may be stable or metastable. Polymorphism in solids gives rise to a difference in crystalline form between polymorphs of the same substance. This difference may produce a change in the dissolution rates of the polymorphs. For example, Wurster and Taylor (1965b) have shown that three crystalline forms of prednisolone exhibit different dissolution behaviours, and Tawashi (1968) has reported a marked difference in the dissolution rates of two polymorphic forms of aspirin. The pharmaceutical applications of polymorphism have been reviewed by Haleblian and McCrone (1969).

3. *Changes in the Characteristics of the Solvent*

(*a*) *Viscosity.* An increase in viscosity of the liquid phase will reduce the rate of diffusion of solutes. It is therefore to be expected that dissolution rates dependent on diffusion will be decreased by an increase in viscosity of the solvent, whereas those that are controlled by reactions at the interface will be little affected by changes in viscosity.

(*b*) *Surface Activity.* It has been postulated that increased dissolution rates obtained in the presence of surface active agents may be caused by a lower interfacial tension, which allows better wetting and penetration by the solvent (Taylor and Wurster, 1965). In addition, changes in the extent of etching of crystal surfaces caused by the presence of surface active agents may lead to increased dissolution rates (Westwood *et al.*, 1962).

The whole subject of dissolution rates has been reviewed by Wurster and Taylor (1965a).

Solubility of Solids in Mixtures of Miscible Liquids

The effect of the addition of a miscible liquid to a solution is of importance in certain pharmaceutical processes and systems. For example, resins are soluble in ethanol but not in water. The former solvent is, therefore, often used in the extraction of resins from crude drugs. The alcoholic solution is then concentrated by evaporation, and the resin is precipitated by pouring into an excess of water. The precipitate can then be collected and washed free from water-soluble impurities. Alcoholic solutions (tinctures) of resins are often used in dispensing practice. If these solutions are diluted with water then the resin is precipitated as a sticky mass. This type of precipitate should be avoided by slowly pouring the resinous tincture into an aqueous dispersion of a protective colloid (p. 61). The mixture should be continuously stirred during this process. The resin should then be precipitated as finely divided particles that are readily dispersible in the aqueous vehicle.

The Distribution of Solutes between Immiscible Liquids

If a substance, which is soluble in both components of a mixture of immiscible liquids, is dissolved in such a mixture, then, when equilibrium is attained at constant temperature, it is found that the solute is distributed between the two liquids in such a way that the ratio of the activities of the substance in each liquid is a constant. This is known as the Nernst distribution law, which can be expressed by Eqn (2.8)—

$$\frac{a_A}{a_B} = \text{constant} \qquad (2.8)$$

where a_A and a_B are the activities of the solute in solvents A and B, respectively. When the solutions are dilute or when the solute behaves ideally, the activities may be replaced by concentrations (c_A and c_B),

$$\frac{c_A}{c_B} = K \qquad (2.9)$$

where the constant K is known as the distribution or partition coefficient. In the case of sparingly soluble substances, K is approximately equal to the ratio of the solubilities (s_A and s_B) of the solute in each liquid; i.e.

$$\frac{s_A}{s_B} = K \qquad (2.10)$$

In most other systems, however, deviation from ideal behaviour invalidates Eqn (2.10).

Association or dissociation of the solute molecules in either solvent should be taken into account, since Eqn (2.9) applies only to an equilibrium between solute molecules in the same state in both liquids. For example, if the solute exists as monomers in solvent A and as dimers in solvent B, the distribution coefficient is given by Eqn (2.11), in which the square root of the concentration of the dimeric form is used:

$$K = \frac{c_A}{\sqrt{c_B}} \qquad (2.11)$$

If the dissociation into ions occurs in the aqueous layer, B, of a mixture of immiscible liquids, then the degree of dissociation (α) should be taken into account as indicated by Eqn (2.12)

$$K = \frac{c_A}{c_B(1 - \alpha)} \qquad (2.12)$$

The solvents, in which the concentrations of the solute—numerators and denominators of Eqns (2.9), (2.11), and (2.12)—are expressed, should be indicated when partition coefficients are quoted. For example, a partition coefficient of 2 for a solute distributed between oil and water may also be expressed as a partition coefficient between water and oil of 0·5.

APPLICATIONS OF THE DISTRIBUTION LAW

1. *Extraction.* Extraction of substances from one phase into another is often used in analytical and organic chemistry and in the removal of active principles from crude drugs. Application of the distribution law to the process of extraction shows that it is more efficient to divide the extracting solvent into a number of smaller volumes that are used in successive extractions rather than to use the total amount of solvent in one single process. (*See* Chapter 22 for more information on extraction, and an example of the method of increasing extraction efficiency.)

2. *Partition Chromatography.* This is a technique used for the separation of components in a mixture. It depends on the difference in the distribution coefficients of the components between two immiscible liquids or between a liquid and a vapour phase. One liquid is maintained stationary by adsorption on to an inert solid support, which may be a powdered solid or strips of a porous material such as filter paper. If a powder is used, then the separation is carried out in a column packed with the powder and its adsorbed liquid phase. The other liquid or vapour is allowed to pass through the column and,

therefore, constitutes a mobile phase. Components of a mixture introduced into the system will become distributed between the mobile and stationary phases in accordance with their partition coefficients, and, provided there is a difference between these coefficients, the components will move at different rates along the column and will eventually become separated.

In paper chromatography, where a filter paper is used to support the stationary liquid phase, the flow of a mobile liquid phase may be made to occur in a vertical or horizontal direction through a strip of paper, or in a radial direction through a paper disc. Whatever the direction of flow the basic principles of the separation technique remain the same as those explained above. More information on the theories and techniques of chromatography is given by Heftmann (1961).

3. *Release of Drugs from Certain Dosage Forms.* Some common dosage forms such as suppositories and ointments are often formulated in water-immiscible bases. The rate of release of medicaments from these dosage forms into aqueous body fluids or secretions will depend on several factors. One of the most important of these is the partition coefficient of the medicament between the base and the body fluid. The effect of partition between water immiscible bases and body fluids is also made use of in the formulation of products intended to provide a prolonged release of drug.

4. *Passage of Drugs through Living Membranes.* The cell membrane is considered to behave as a lipoidal barrier surrounding the cells. One of the main routes of penetration of drugs into cells therefore involves the partition of the substances between these lipoidal layers and the aqueous body fluids with which they are in contact. The partition coefficient of the drug is therefore important in all processes that involve the transport and distribution of drugs throughout the body; e.g. the absorption of drugs from the gastro-intestinal tract, distribution of drugs between various tissues, and penetration of drugs to the sites where they can exert their pharmacological activity (*see* Chapter 6 for more information).

The uptake of preservatives and other substances by micro-organisms is also influenced by the partition coefficient of the compound between the cells and the surrounding aqueous phase (*see* Chapter 31).

5. *Preservation of Emulsions and Creams.* Emulsions and creams are systems comprised of two immiscible phases, one of which is dispersed as globules throughout the other. Micro-organisms usually multiply in the aqueous phase of this type of system, and preservatives must therefore be capable of exerting their activity in this phase. However, most preservatives are usually soluble in both oil and water and will be distributed between these two phases in an emulsion and cream. This distribution will affect the concentration of the substance in the aqueous phase and should be taken into account when deciding the overall concentration of preservative to be used in these systems (*see* Chapter 31).

6. *The Formulation of Solubilised Systems.* Use is often made of compounds known as solubilising agents as a means of increasing the apparent water solubility of organic compounds in the formulation of pharmaceutical preparations. The process is known as solubilisation and it may be regarded as a partition of the organic compound between the interior of the colloidal aggregates (micelles p. 64) formed by the solubilising agents and the surrounding aqueous phase. The activity of the solubilised compound is related to its concentration in the aqueous phase, and a knowledge of the partitioning effect therefore becomes necessary for the proper formulation of such preparations.

7. *Determination of Equilibrium Constants for the Formation of Intermolecular Complexes.* If an intermolecular complex is formed in one phase of an immiscible liquid mixture between a solute *A* that is only soluble in that phase and a second solute *B* that is soluble in both phases, then the partition coefficient of the latter will differ from the value that is observed in the absence of *A*. This change in partition coefficient may be used to determine the equilibrium constant for the formation of the intermolecular complex. This method has been used by Higuchi and his co-workers (1969) to determine the equilibrium constants for a variety of complexes involving compounds of pharmaceutical interest.

Colligative Properties of Solutions

These are the physical properties of a solution that depend on the proportion of dispersed solute particles that are present in the solution. The colligative properties arise from the attractive forces that are exerted by the solute on the solvent. For example, such attractive forces reduce the tendency of the solvent to escape from the liquid as a vapour, and the vapour pressure of the solvent is therefore reduced by the presence of a solute.

The other colligative properties are: (*a*) the elevation of boiling point, (*b*) the depression of freezing point, and (*c*) the osmotic properties. The last of these properties is the most important from a

pharmaceutical point of view and the implications of this effect are given by Gunn and Carter (1965).

BIBLIOGRAPHY

BARROW, G. M. (1966) *Physical Chemistry*. 2nd ed. McGraw-Hill, London.

GUCKER, F. T. and SEIFERT, R. L. (1967) *Physical Chemistry*. English Universities Press, London.

HILDEBRAND, J. H. and SCOTT, R. L. (1962) *Regular Solutions*. Prentice Hall Inc., New Jersey.

HOOVER, J. E. (Ed.) (1970) *Remington's Pharmaceutical Sciences*. 14th ed. Chapter 19, Mack Publishing Co., Pennsylvania.

MARON, S. H. and PRUTTON, C. F. (1958) *Principles of Physical Chemistry*. 3rd ed. Macmillan, New York.

MARTIN, A. N., SWARBRICK, J. and CAMMARATA, A. (1969) *Physical Pharmacy*. 2nd ed. Henry Kimpton, London.

ROSE, J. (1961) *Dynamic Physical Chemistry*. Pitman, London.

REFERENCES

BUCKLEY, H. E. (1951) *Crystal Growth*. pp. 29–31. Wiley, New York.

GUNN, C. and CARTER, S. J. (1965) *Dispensing for Pharmaceutical Students*. 11th ed. Pitman Medical, London.

HALEBLIAN, J. and MCCRONE, W. (1969) Pharmaceutical applications of polymorphism. *J. pharm. Sci.*, **58**, 911–929.

HEFTMANN, E. (1961) *Chromatography*. Reinhold, New York.

HIGUCHI, T., RICHARDS, J. H., DAVIS, S. S., KAMADA, A., HOU, J. P., NAKANO, M., NAKANO, N. I., and PITMAN, I. H. (1969) Solvency and hydrogen bonding interactions in non-aqueous systems. *J. pharm. Sci.*, **58**, 661–671.

KOSTENBAUDER, H. B. and HIGUCHI, T. (1956) Formation of molecular complexes by some water soluble amides. I. Interaction of several amides with *p*-hydroxybenzoic acid, salicylic acid, chloramphenicol, and phenol. II. Effect of decreasing water solubility on degree of complex formation. *J. pharm. Sci.*, **45**, 518–522 and 810–813.

MCGLASHAN, M. L. (1968) *Physico-chemical Quantities and Units*. Monographs for teachers, No. 15, Royal Institute of Chemistry, London.

TAWASHI, R. (1968) Aspirin: Dissolution rates of two polymorphic forms. *Science*, **160**, 76.

TAYLOR, JR., P. W. and WURSTER, D. E. (1965) Dissolution kinetics of certain crystalline forms of prednisolone. II. Influence of low concentrations of sodium lauryl sulphate. *J. pharm. Sci.*, **54**, 1654–1658.

WESTWOOD, A. R. C., OPPERHAUSER JR., H., and GOLDHEIM, D. L. (1962) Anomalous solution and etching phenomena. *J. appl. Phys.*, **33**, 1764–1766.

WURSTER, D. E. and KILSIG, D. O. (1965) Effect of complex formation on dissolution kinetics of *m*-aminobenzoic acid. *J. pharm. Sci.*, **54**, 1491–1494.

WURSTER, D. E. and TAYLOR JR., P. W. (1965a) Dissolution rates. *J. pharm. Sci.*, **54**, 169–175.

WURSTER, D. E. and TAYLOR JR., P. W. (1965b) Dissolution kinetics of certain crystalline forms of prednisolone. *J. pharm. Sci.*, **54**, 670–676.

3

Phase Equilibria

A PROPER understanding of certain systems and processes that are encountered in pharmaceutical practice necessitates a knowledge of the principles that govern the equilibria between solid, liquid, and gaseous phases.*

The Phase Rule

The conditions relating to physical equilibria between various states of matter are conveniently expressed by the Phase Rule, which was derived by J. Willard Gibbs in 1876. In order to understand this rule it is first necessary to explain what is meant by the terms 'phase', 'number of components', and 'degrees of freedom'.

PHASE

A phase is defined as any homogeneous and physically distinct part of a system that is separated from other parts of the system by definite boundaries. For example, ice, water, and water vapour are three separate phases; each is physically distinct and there are definite boundaries between them. Pure liquids or solutions constitute homogeneous phases, but two immiscible liquids (or solutions) constitute two phases since there is a definite boundary between them. A mixture of gases always constitutes one phase because the mixture is homogeneous and there are no bounding surfaces between the different gases in the mixture.

NUMBER OF COMPONENTS

The number of components of a system is the smallest number of independent chemical constituents necessary to express the concentration of all phases present in the system. For example, in the three-phase system ice, water, and water vapour, the number of components is one, since each phase can be expressed in terms of H_2O. A mixture of salt and water is a two component system since both chemical species are independent.

DEGREES OF FREEDOM

The number of degrees of freedom is the number of variable conditions such as temperature, pressure, and concentration that it is necessary to state in order that the condition of the system at equilibrium may be completely defined. The significance of the number of degrees of freedom of a system will be better understood after considering the specific equilibria that are discussed in the succeeding sections on phase equilibria.

The relationship between the number of phases, P, components, C, and degrees of freedom, F, for equilibria that are influenced only by temperature, pressure, and concentration is given by Eqn (3.1) which is a quantitative expression of the Phase Rule.

$$F = C - P + 2 \qquad (3.1)$$

The application of Eqn (3.1) to various systems of pharmaceutical interest will obviously depend on the number of components present in individual systems. For the convenience of discussing these systems, it is therefore better first to consider those with one component only, and then to move on to those with two components. The succeeding sections are therefore based on such a division, and in each case an attempt will be made to discuss a range of pharmaceutical systems that are examples of each category.

In these discussions the effects of temperature, pressure and composition on the phase equilibria will be indicated by graphs called phase diagrams, which show the variation of a transition temperature such as a boiling point or a melting point with pressure or composition. Representation of the simultaneous effect of three variables would require three axes. This can be achieved with three-dimensional models but if one variable is fixed the resulting planar diagram can be regarded as a section through such a model. The difficulties associated with the representation of three variables do not arise in systems containing one component because

* It is assumed that the student is familiar with the kinetic theory of matter and the properties of solids, liquids, and gases.

no variation in the compositions of these systems can occur. It is therefore sufficient to consider only the effects of variation in temperature and pressure.

SYSTEMS OF ONE COMPONENT

The phase diagram for the ice–water–water vapour system (Fig. 3.1) may be used to illustrate the interpretation of these diagrams for one-component systems. This particular diagram is also of importance in the understanding of the process of freeze drying.

In a diagram such as Fig. 3.1, the areas each correspond to a single phase. The number of degrees of freedom is therefore given from Eqn (3.1) as

$$F = 1 - 1 + 2 = 2$$

This means that temperature and pressure can be varied independently within these areas. For example, by varying the temperature and pressure, a mass of water under conditions corresponding to point w_1 in Fig. 3.1 may be converted to a mass at higher temperature and pressure at point w_2; i.e. this independent variation of temperature and pressure has not altered the number of phases in the system. However, if the conditions are such that the system corresponds to a point that lies on one of the lines *AO*, *BO*, or *CO*, then two phases now exist in equilibrium with each other, since these lines form the boundaries between different phases. The number of degrees of freedom is reduced, because, from Eqn (3.1) $F = 1 - 2 + 2 = 1$. This means that a single variable exists when equilibrium is established between two phases, and if the pressure is altered the temperature will assume a particular value or, conversely, if the temperature is altered the pressure will have a definite value.

Melting Points

The boundary *BO* represents the coexistence of liquid water and solid ice at various temperatures and pressures. *BO* therefore indicates the effect of pressure on the melting point of ice, and the negative slope of this line shows that the melting point decreases as the pressure increases. If at any point on this line the pressure is increased while the temperature is maintained constant, then all the ice will be converted to liquid water; i.e. only one phase will remain instead of the two original phases that were in equilibrium at the point on *BO*. Thus, in order to maintain equilibrium conditions between the two phases, the temperature and pressure must not be varied independently of each other.

Boiling Points

The boundary *CO*, which is known as the vapour pressure curve, represents the coexistence of liquid water and water vapour under various conditions.

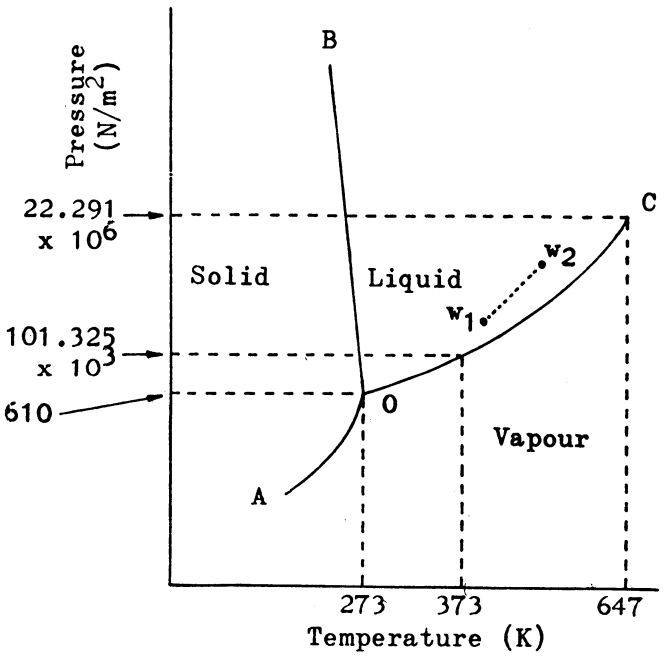


Fig. 3.1 Phase diagram for water at moderate temperatures and pressures (not drawn to scale)

The temperature and pressure again cannot be varied independently otherwise a change from a two-phase system to a single-phase system will occur. For example, if the pressure is kept constant at any point along *CO* while the temperature is increased, then all the water will be converted to vapour and only one phase will remain. *CO* therefore represents the effect of pressure on the boiling point of water and it has an upper limit at the critical temperature of water (647 K*). This is the temperature above which it is impossible to liquefy water vapour.

Equilibria that involve vapours are affected appreciably by variation in pressure. Tabulated boiling points should therefore be quoted at a definite pressure (usually atmospheric pressure, i.e. $1{\cdot}013\,25 \times 10^5$ N/m^2), and experimentally obtained values should be converted to values at the appropriate pressure for the purposes of comparison with previously reported ones. Changes in the boiling point of a compound may be calculated from Eqn (3.2), which is known as the Clapeyron equation. (The derivation of this is given in most textbooks of physical chemistry—*see* Bibliography.)

$$\frac{dT}{dp} = \frac{T(V^{G} - V^{L})}{L_{V}} \qquad (3.2)$$

In Eqn (3.2), V^{G} and V^{L} are the volumes occupied by one mole of the gas and liquid, respectively, L_{V} is the latent heat of vaporisation of the liquid, T is the thermodynamic temperature, and dT/dp is the change in boiling point with pressure.

A similar Eqn (3.3) can be used to calculate the effect of pressure on melting points, and in this equation V^{S} is the volume occupied by one mole of the solid, L_t is the latent heat of fusion of the solid, dT/dp is the change in melting point with pressure, and the remaining terms are defined as before:

$$\frac{dT}{dp} = \frac{T(V^{L} - V^{S})}{L_{t}} \qquad (3.3)$$

Since the equilibrium at a melting point does not involve vapour, then the effect of pressure is very small compared with the effect on boiling points.

Triple Points

In Fig. 3.1 the boundary lines meet at *O*, which is the only point in the diagram where three phases may coexist in equilibrium and it is therefore termed a triple point. The application of the Phase Rule equation to the system at *O* shows that

$$F = 1 - 3 + 2 = 0$$

The system is therefore invariant; i.e. any change in pressure or temperature will result in an alteration of the number of phases that are present.

The triple point for water occurs at a temperature of 273·159 8 K and a pressure of 610 N/m^2. Thus, the triple point temperature is 0·009 8°C above the usual freezing point of water at $1{\cdot}013\,25 \times 10^5$ N/m^2. However, application of Eqn (3.3) will show that a change in pressure from 610 N/m^2 to $1{\cdot}013\,25 \times 10^5$ N/m^2 will produce a decrease in the freezing point of water of only 0·007 5°C. The difference between this calculated value and the observed value is caused by the common presence of air dissolved in water.

Sublimation and Sublimation (Freeze) Drying

The boundary *AO*, which is known as the sublimation pressure curve for ice, indicates the conditions for the coexistence of vapour and solid phases in equilibrium. A mass of ice may be converted directly into water vapour by heating, provided that the pressure is kept below the triple point pressure. This transition is particularly valuable in drying compounds that are sensitive to the higher temperatures usually associated with drying techniques. Removal of water by means of sublimation is termed sublimation or freeze drying and the importance of the triple point in this process should be appreciated at this stage. Further information on the actual drying process is given in Chapter 24.

Polymorphism

Some substances can exist in more than one type of crystal structure. This ability is known as polymorphism and the different structures are termed polymorphs. If the substance is an element then the phenomenon is called allotropy instead of polymorphism.

A reversible change from one polymorph to another frequently occurs at a definite temperature, and both structures can therefore exist in equilibrium at this temperature. Crystalline forms that exhibit this type of behaviour are said to be enantiotropic. For example, the rhombic crystal structure, which is the stable form of sulphur at ordinary temperatures, is converted to the monoclinic structure at 368·5 K, and the transition is reversed at this point on cooling from a higher temperature. Since each enantiomorph represents a separate phase, the number of degrees of freedom that exist when equilibrium is established between them is restricted

* The freezing point of water on the thermodynamic temperature scale is equal to 273·15°C. This value has been approximated to 273°C in this chapter unless stated otherwise.

to one, and the transition temperature is therefore affected by pressure. Thus, in a system containing a solid that is able to exist as two polymorphs, an additional line is required in the phase diagram to represent the boundary between the two solid forms. The inclusion of an extra boundary increases the number of triple points in a phase diagram. The sulphur phase diagram is the classical example of such a system and the Bibliography should be consulted for an explanation of this diagram. The phase diagram of water at very high pressures could, in fact, be used to illustrate the phenomenon of polymorphism, because ice may exist in several different forms. However, this would not be very satisfactory as a simple illustration owing to the rather complicated nature of the phase diagram of water under these conditions.

In some cases the change from one polymorphic form to another occurs in one direction only and reversion is not possible in a direct manner. Substances that exhibit this type of polymorphism are termed monotropic. For example, diamond can be converted directly into graphite but the reverse process is not directly possible.

The polymorphic changes between the crystalline forms of fatty acids and glycerides are nearly always monotropic. Theobroma oil, which is used in the preparation of suppositories, is a polymorphous, natural substance. It consists mainly of a single glyceride and usually melts over a narrow temperature range (34 to 36°C), which is just below normal body temperature. The four polymorphic forms of this substance are shown in Table 3.1 together with

Table 3.1
The Polymorphic Forms of Theobroma Oil

Polymorph	*m.p.* (°C)
Metastable γ form	18
Metastable α form	22
Metastable β' form	24
Stable β form	34·5

their melting points. If, during the course of preparation of suppositories, theobroma oil is heated to about 35°C or above and completely liquefied, then the resulting suppositories are too soft for proper administration and tend to melt at ordinary room temperatures. It has been pointed out (Riegelman, 1955) that the excessive heating will cause complete destruction of the nuclei of the stable β form. Consequently, the mass tends to supercool to about 15°C before crystallisation reoccurs in the form of the metastable α, β', and γ forms with a melting point of 22 to 24°C. If the initial heating is limited to about 33°C the mass is sufficiently fluid for pouring, but the nuclei of the stable β form are preserved and cause the separation of β crystals with a melting point of 34·5°C on cooling.

Polymorphism may also be exhibited by liquids. For example, cholesteryl acetate melts to produce a turbid liquid which becomes clear at a higher transition temperature. The turbid and clear forms of polymorphic liquids have different optical properties and the turbid forms have been referred to as liquid crystals, although the terms anisotropic or mesomorphic liquids are preferable. The transition temperature for the change from mesomorphic liquid to clear liquid is pressure dependent.

The different crystal structures of polymorphic forms of the same substance will cause a difference in the thermodynamic activities of the polymorphs (Higuchi and co-workers, 1963). This is of importance in pharmacy, since many drugs exhibit polymorphism and their activities will govern their stabilities and their rates of solution. Thus, one polymorph may be more stable than others. In addition, one may show a greater rate of solution and may therefore be absorbed from the gastrointestinal tract at a greater rate than other forms, and so produce a higher plasma concentration. For example, the effect of polymorphism on the availability of methylprednisolone and sulphathiazole has been investigated by Higuchi and his co-workers (1963, 1967), and Aguiar and his co-workers (1967) have shown that the polymorphic state of chloramphenicol palmitate has a significant influence on the blood levels of chloramphenicol in humans. If the existence of polymorphism is unrecognised, then the possibility of variation in the availability of a given drug from successive doses may arise. The pharmaceutical applications of polymorphism have been reviewed by Haleblian and McCrone (1969).

SYSTEMS OF TWO COMPONENTS

Table 3.2 shows the effect of the number of phases on the degrees of freedom in a two-component system. When one phase only is present there are

Table 3.2
The Degrees of Freedom in Two-component Systems

P	*F*
1	3
2	2
3	1
4	0

three degrees of freedom; i.e. temperature, pressure, and composition. Thus, the behaviour of a two component system may be represented completely only by a three-dimensional diagram showing the relations between the three variables. However, it is more convenient to use separate two-dimensional diagrams which show the relation between two of the variables while the third is kept constant; e.g. diagrams showing the variation of pressure with composition at constant temperature, or the variation of composition with temperature at constant pressure.

Solid-Vapour Systems of Two Components

The conversion of an anhydrous salt to a hydrated form, the transition of one hydrated form to a higher hydrate, and the phenomena of deliquescence, hygroscopicity, efflorescence, and exsiccation are examples of the equilibria in systems containing a solid and water vapour.

HYDRATION AND DEHYDRATION OF SALTS

Each hydrated form of a salt exerts a definite vapour pressure at a given temperature. The relation between this value and that of the vapour pressure of water vapour in the atmosphere surrounding the salt is of importance in deciding the type of hydrate formed under various conditions.

EFFLORESCENCE AND EXSICCATION

If the vapour pressure of a hydrated salt is greater than the pressure exerted by the water vapour in the surrounding atmosphere then the salt will attempt to attain equilibrium with its surroundings, and therefore tend to lose water to form a lower hydrate or an anhydrous salt. This phenomenon is known as efflorescence.

The pressure of water vapour in the atmosphere is about $13{\cdot}33 \times 10^2$ N/m^2 at 293 K, and therefore hydrates with vapour pressures greater than this will tend to exhibit efflorescence and be unstable, provided that the lower hydrate that is formed still exerts a vapour pressure greater than the surrounding atmosphere. If this is not so, then water will be taken up from the atmosphere by the lower hydrate as fast as it is formed and the final equilibrium will depend on the rates at which water is lost or taken up by the two hydrates. For example, the behaviour of the various forms of sodium carbonate may be represented by the following scheme—

$Na_2CO_3.10\,H_2O$ v.p. $= 32 \times 10^2$ N/m^2 at 293 K

↓ spontaneous dehydration; i.e. efflorescence.

$Na_2CO_3.H_2O$ v.p. $= 16 \times 10^2$ N/m^2 at 293 K

↑ efflorescence not observable because anhydrous salt is rapidly hydrated.

Na_2CO_3 (anhyd.) v.p. $= 0$

Since the vapour pressure exerted by the decahydrate is much greater than that of normal atmosphere it loses water by the process of efflorescence and is converted to the monohydrate. The vapour pressure of the latter is still above that of the atmosphere, but further apparent loss of water does not occur since the anhydrous salt is rehydrated at a faster rate than dehydration of the monohydrate.

The vapour pressure of hydrated salts, and therefore the rate of efflorescence, increases with rise in temperature. The process of accelerating the rate of efflorescence by increasing the temperature in order to remove water of crystallisation from a hydrated salt is known as exsiccation, although this term is also used where water is not normally lost by efflorescence. For example, the pentahydrate of copper sulphate may be converted to the trihydrate by heating to 303 K. Two further molecules of water are removed at 373 K to yield the monohydrate, and the remaining molecule of water is removed at 473 K to yield the anhydrous salt.

Since the instability that arises from efflorescence is caused by the loss of water vapour, the common method of minimising such deterioration involves the use of containers that prevent the loss of water vapour. The additional precautions of using well-filled containers with a minimum amount of atmosphere above the efflorescent material and storage in a cool place are also advisable.

DELIQUESCENCE AND HYGROSCOPICITY

Both of these terms are used to indicate that a material takes up water vapour from the atmosphere and is converted to a more hydrated form. In the case of a hygroscopic substance the more hydrated state is still a solid but deliquescence implies the eventual formation of a liquid phase; i.e. a solution. In both phenomena, however, the final more hydrated state must still exert a lower vapour pressure than that of the water vapour in the surrounding atmosphere. If this is not so then the newly formed hydrated state will immediately lose water by efflorescence and revert to the initial state.

Thus, for a liquid phase to be produced by deliquescence, it is necessary that the vapour pressure exerted by a saturated solution of the deliquescent material should be less than $13{\cdot}33 \times 10^2$ N/m^2. The following scheme showing the behaviour of sodium hydroxide may be used as an example of deliquescence.

$NaOH.H_2O$ v.p. is very low at 293 K

↓ Deliquescence

Saturated solution of NaOH v.p. = $1{\cdot}33 \times 10^2$ N/m^2 at 293 K

↓ Further deliquescence

Unsaturated solution of NaOH v.p. = v.p. of atmospheric moisture

Other deliquescent materials include potassium hydroxide, sodium lactate and potassium carbonate, while examples of hygroscopic materials include exsiccated sodium sulphate, ammonium chloride, and squill.

Storage precautions for pharmaceutical preparations that are deliquescent or hygroscopic are aimed at the maintenance of a moisture-free atmosphere inside the container. The closures of the latter should therefore prevent the access of water vapour, and official monographs usually direct that such substances should be stored in 'well-closed' containers. In addition, a well-filled container limits the volume of atmosphere in the container and, therefore, further reduces the uptake of moisture by the product. In certain cases, where the product is particularly susceptible to moisture, a drying agent may be placed inside the container. The drying agent is usually contained in small packets, made from a material that is pervious to water vapour, in order to prevent contact between the agent and the product. Silica gel is often used in this way and it may contain an indicator to show when its drying properties are no longer satisfactory. Anhydrous cobaltous chloride, which is blue, may be used as an indicator, since it is converted to a pink hydrate when the silica gel has adsorbed its maximum amount of water vapour.

Liquid-Liquid Systems of Two Components; Solutions of Liquids in Liquids

The degree of miscibility of two liquids may be used as a basis for the classification of these systems into the following types:

1. Completely miscible liquids.
2. Partially miscible liquids.
3. Immiscible liquids.

1. COMPLETELY MISCIBLE LIQUIDS

A solution of one liquid in another in contact with vapour from the liquid mixture constitutes a two-phase system of two components. The Phase Rule therefore indicates that such a system will possess two degrees of freedom; i.e.

$$F = 2 - 2 + 2 = 2.$$

Thus, the system will be completely defined by two variables. For example, if the temperature and composition are fixed, the vapour pressure must have a definite value, or if the pressure and composition are fixed then the equilibrium will only be maintained at a particular temperature.

In diagrams involving vapour pressures exerted by solutions of liquids in liquids it is necessary to consider the application of Raoult's law. This states that the partial vapour pressure exerted by each component is proportional to its molar concentration in the solution. The law may be expressed by Eqn (3.4):

$$p = p_A + p_B = p_A^0 x_A + p_B^0 x_B \qquad (3.4)$$

where p is the total vapour pressure above a liquid mixture containing x_A and x_B mole fractions of components A and B, respectively, p_A^0 and p_B^0 are the vapour pressures exerted by the pure components, and p_A and p_B are the partial vapour pressures exerted by the components in the liquid mixture.

Ideal Solutions. Raoult's law is obeyed by only a few solutions of liquids in liquids. However, it is convenient to consider an ideal solution, to which this law applies, and to discuss real solutions in terms of the deviations in their behaviour from that of an ideal solution.

A graph showing the variation in the partial pressure of each component in an ideal solution, with the composition of the solution at constant temperature, should produce a straight line which passes through the origin, since $p_A = p_A^0 x_A$ and $p_B = p_B^0 x_B$. The line for each component can be represented on the same diagram as shown in Fig. 3.2, where $O_A p_A^0$ and $O_B p_B^0$ indicate the variations in partial pressures exerted by components A and B, respectively, with the composition of the mixture. From Eqn (3.4), and by applying simple geometry, it can be shown that the line $p_A^0 p_B^0$ will indicate the variation in the total vapour pressure with composition.

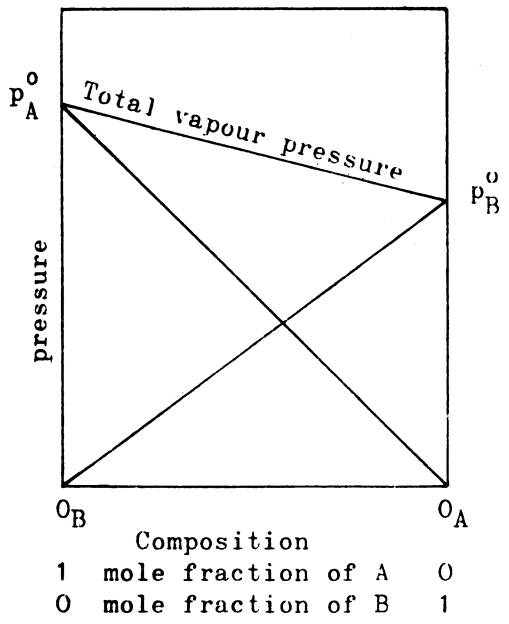


Fig. 3.2 Vapour-composition diagram for an ideal solution

Real Solutions. As previously stated, only a few actual solutions show ideal behaviour. The components of these ideal solutions have a similar chemical structure; e.g. benzene and toluene, *n*-hexane and *n*-heptane, ethyl bromide and ethyl iodide.

Most systems show varying degrees of deviation from Raoult's law, depending on the nature of the liquids and on the temperature. When interactions such as hydrogen bonding, salt formation, or hydration occur between the components of a solution, then the vapour pressure of each component is lowered with respect to the behaviour of an ideal solution and the system is said to exhibit a negative deviation from Raoult's law; e.g. chloroform and acetone, pyridine and acetic acid, water and nitric acid.

In most systems, the vapour pressures are greater than those of an ideal solution and positive deviations from Raoult's law are therefore exhibited. This type of behaviour occurs when the components differ in their polarity, length of hydrocarbon chain, and degree of association; e.g. carbon tetrachloride and cyclohexane, benzene and ethanol, water and ethanol. The degree of deviation from Raoult's law decreases as the temperature increases, since the effects of the differences in the natures of the components are reduced at higher temperatures. Conversely, a decrease in temperature may lead to a decrease in miscibility of the two components and phase separation may occur.

The occurrence of deviations from ideal behaviour allows the classification of solutions of liquids in liquids into three types.

(*a*) Systems where the total vapour pressure is always intermediate between those of the pure components; i.e. there is neither a maximum nor minimum in the vapour pressure-composition diagram as shown in Fig. 3.3(*a*). These systems are known as zeotropic mixtures and examples include carbon tetrachloride and cyclohexane, and water and methanol.

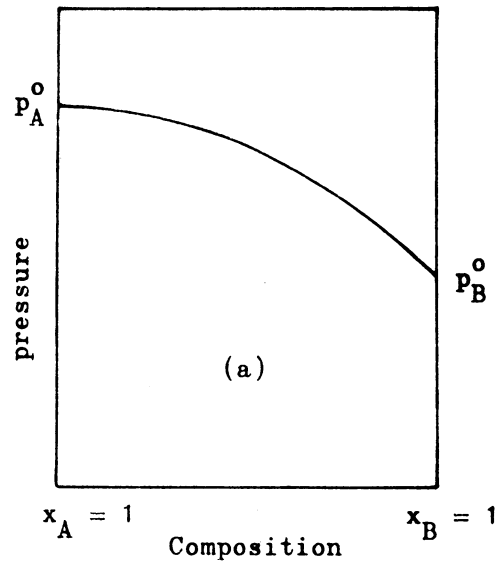
(*b*) Systems that exhibit a maximum value in the vapour pressure-composition diagrams as shown in Fig. 3.3(*b*). These are known as azeotropic mixtures with a maximum vapour pressure or minimum boiling point and examples include benzene and ethanol, and water and ethanol.

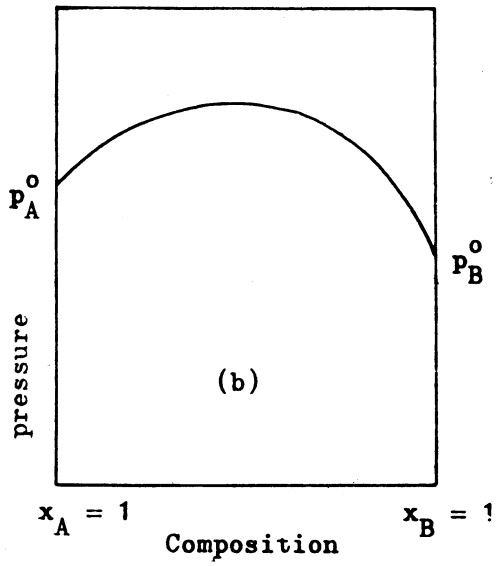
(*c*) Systems that exhibit a minimum value in the vapour pressure-composition diagrams as shown in Fig. 3.3(*c*). These are known as azeotropic mixtures with a minimum vapour pressure or maximum boiling point. and examples include chloroform and acetone, pyridine and acetic acid, and water and nitric acid.

The effects of these different types of behaviour on the results of distillation of liquid mixtures is of importance in various pharmaceutical fields. However, before these distillations can be considered, it is necessary to take into account the composition of the vapour that is in equilibrium with the liquid mixtures of different compositions. The previous vapour pressure diagrams show only the relation between vapour pressure and composition of the liquid phase. If these diagrams are drawn to show the variation in vapour pressure with both vapour and liquid compositions, the results may be represented by Fig. 3.4(*a*), (*b*), and (*c*), respectively.

The upper curves in these figures represent the variation in total vapour pressure with composition of the liquid phase, and the lower curves represent the variation in total vapour pressure with composition of the vapour phase. The different areas correspond to the existence of liquid, vapour, or liquid plus vapour, as shown in the diagrams.

When equilibrium is established between liquid and vapour phases the vapour pressure must be constant. It can therefore be seen that the compositions of the vapours (v_1 to v_5) that are in equilibrium with liquids of compositions given by l_1 to l_5 are obtained by drawing horizontal tie-lines through the points on the liquid composition curves that correspond to l_1 to l_5. The points at which these lines intersect the vapour curves provide the compositions





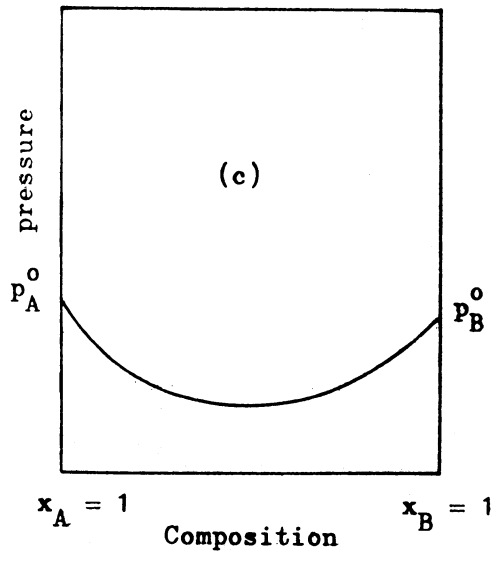


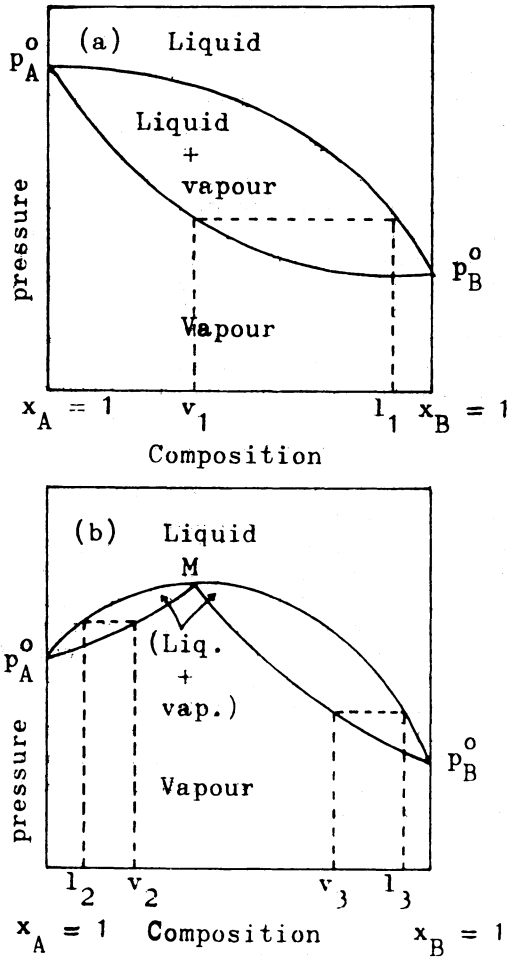
Fig. 3.3 Effect of deviation from ideal behaviour on total vapour pressures of various liquid mixtures
(*a*) zeotropic mixture
(*b*) azeotropic mixture with a maximum vapour pressure
(*c*) azeotropic mixture with a minimum vapour pressure

v_1 to v_5. It can be seen from Fig. 3.4(*a*) that the vapour phase in equilibrium with a particular liquid composition is richer in the more volatile component *A*; i.e. the component with the higher vapour pressure. This is known as Konowaloff's Rule.

The point *M* in Fig. 3.4(*b*) and (*c*) corresponds to the formation of an azeotrope, which is a mixture with a lower or higher vapour pressure than is exerted by any other composition in the system. It will be observed that the liquid and vapour have identical compositions at this point.

Distillation of Solutions of Liquids in Liquids

(*a*) *Zeotropic Mixtures.* For the purpose of explaining the effects of distillation it is more convenient to use a phase diagram (Fig. 3.5) that shows the variation in boiling point with composition of the liquid and vapour phases at constant pressure. It should be observed that the upper and lower curves in Fig. 3.5 represent the vapour composition and the liquid composition, respectively, and that the areas corresponding to liquid and vapour phases are



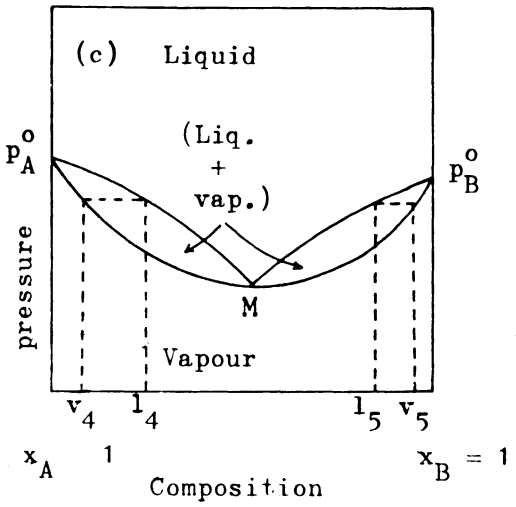


Fig. 3.4 Vapour pressure diagrams showing liquid and vapour composition curves for various liquid mixtures
(*a*) zeotropic mixture
(*b*) azeotropic mixture with a maximum vapour pressure
(*c*) azeotropic mixture with a minimum vapour pressure

transposed when compared with the vapour pressure diagrams shown in Fig. 3.4(*a*). Konowaloff's Rule can still be seen to apply in the boiling point diagram, since a liquid with a composition corresponding to l_1 will boil at temperature T_1 and be in equilibrium with vapour of composition l_2. This vapour is therefore richer in component *A*, which has the lower boiling point (T_A) and is therefore the more volatile component of the liquid mixture.

It can also be seen from Fig. 3.5 that if the vapour of composition l_2 is removed and condensed it will give a liquid of composition l_2. If this liquid is subsequently heated it will boil at temperature T_2 to provide a vapour of composition l_3 that is even richer in component *A*; i.e. the composition of the distillate will approach closer to pure *A* as more stages of heating and condensation are involved. Conversely, as vapour that is richer in *A* is removed from the distillation flask the composition of the liquid remaining in the flask gradually approaches pure *B*. Thus, the components of a zeotropic mixture may be separated completely by the process of fractional distillation, which involves the occurrence of many individual stages of vaporisation and condensation in a distillation column. (*See* Chapter 23 for more information on distillation as a unit operation.)

If the Phase Rule is applied to the two-component system in the distillation flask where two phases (i.e. liquid and vapour) are present, it can be shown that two degrees of freedom exist:

$$F = 2 - 2 + 2 = 2$$

Since the pressure is kept constant, the temperature will therefore change as the composition varies in order to maintain the same number of phases; i.e.

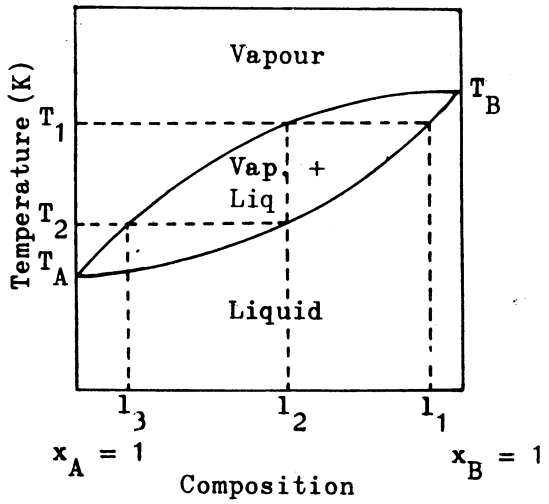


Fig. 3.5 Boiling point-composition diagram for a zeotropic system

the boiling point of the liquid remaining in the flask increases as its composition approaches pure *B*.

(*b*) *Azeotropic Mixtures with a Maximum Boiling Point.* The boiling point diagram for this type of system may be represented by Fig. 3.6(*a*). The same sequence of events and the same reasoning that was involved in the distillation of a zeotropic mixture may be applied to Fig. 3.6(*a*), taking a liquid with a composition on either side of that corresponding to *M* as the starting point. It will be found that a complete separation into pure *A* and pure *B* cannot be achieved whatever the initial composition of the liquid mixture. This is because the liquid and vapour composition curves are coincident at *M*, and a liquid with a composition corresponding to this point boils at a maximum temperature for the system and produces a vapour with the same composition. These mixtures can therefore be separated only by fractional distillation into pure *A* or pure *B*, as the distillate, and a constant boiling mixture of composition *M*, which remains in the distillation flask. The nature of the distillate (i.e. *A* or *B*) depends on the composition of the initial mixture with respect to that of the constant boiling azeotropic mixture.

(*c*) *Azeotropic Mixtures with a Minimum Boiling Point.* The boiling point diagram for this type of system is shown in Fig. 3.6(*b*). Fractional distillation of these mixtures will allow separation of the mixture into pure *A* or pure *B* only, and a constant boiling mixture with a composition corresponding to *M*. Pure *A* or *B* will remain in the distillation flask after the constant boiling mixture has been completely removed at a minimum boiling point. The nature of the pure liquid obtained in the flask (i.e. *A* or *B*) will depend on the composition of the initial mixture with respect to that of the constant boiling azeotrope.

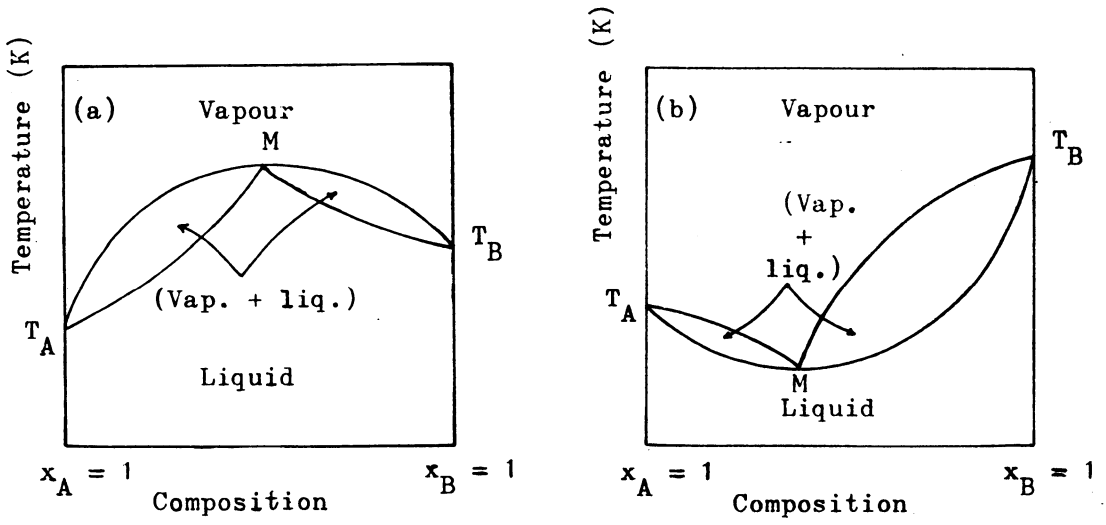


Fig. 3.6 Boiling point-composition diagrams for azeotropic mixtures
(*a*) maximum boiling point azeotrope (*b*) minimum boiling point azeotrope

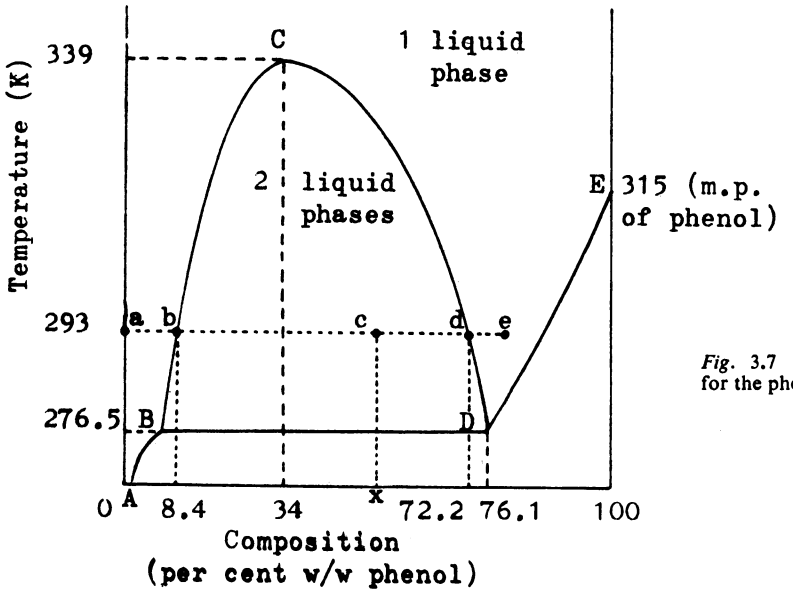


Fig. 3.7 Temperature-composition diagram for the phenol-water system (at 101 325 N/m²)

2. PARTIALLY MISCIBLE LIQUIDS

These systems may be divided into the following types for the convenience of discussion.

(*a*) *Systems Showing an Increase in Miscibility with Rise in Temperature.* A positive deviation from Raoult's law arises from a difference in the cohesive forces that exist between the molecules of each component in a liquid mixture. This difference becomes more marked as the temperature decreases and the positive deviation may then result in a decrease in miscibility sufficient to cause the separation of the mixture into two phases. Each phase consists of a saturated solution of one component in the other liquid. Such mutually saturated solutions are known as conjugate solutions.

The equilibria that occur in mixtures of partially miscible liquids may be followed either by shaking the two liquids together at constant temperature and analysing samples from each phase after equilibrium has been attained, or by observing the temperature at which known proportions of the two liquids, contained in sealed glass ampoules, become miscible, as shown by the disappearance of turbidity.

Phenol-Water System. The temperature-composition diagram of phenol and water at constant pressure (Fig. 3.7) is convenient to use in the explanation of the effects of partial miscibility in systems that show an increase in miscibility with rise in temperature.

The areas shown in Fig. 3.7 each correspond to the existence of various phases as shown in the diagram. The most important part of the diagram, for the purpose of the present discussion, is that indicated by the line *BCD*, which separates a single-phase system of one liquid from a two-phase system of two mutually saturated liquids. If gradually increasing amounts of phenol are added to water at 293 K, the composition moves along the line *abcde*. Between *a* and *b* there is only one liquid phase, and application of the Phase Rule shows that there are three degrees of freedom:

$$F = 2 - 1 + 2 = 3$$

This means that temperature and composition must be specified in order to define the system completely at constant pressure. The aqueous solution is eventually saturated at a composition corresponding to *b* (containing 8·4 per cent phenol). The line *BC* therefore represents the effect of temperature on the solubility of phenol in water. If more phenol is added, then a second layer separates. This is a saturated solution of water in liquid phenol. Thus, at a total composition corresponding to point *c* (i.e. containing *x* per cent phenol) two conjugate solutions will exist as separate phases. The compositions of these phases will correspond to points *b* and *d* respectively (i.e. one solution contains 8·4 per cent phenol in water and the other contains 27·8 per cent water in phenol). The relative amounts of these