

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)—

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

where,  $d$  is the mean diameter of the particles,  $m$  is the mass of the particles, and  $\rho$  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 Haleblan 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).

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

<i>Polymorph</i>	<i>m.p. (°C)</i>
Metastable $\gamma$ form	18
Metastable $\alpha$ form	22
Metastable $\beta'$ form	24
Stable $\beta$ 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  $\beta$  form. Consequently, the mass tends to supercool to about 15°C before crystallisation reoccurs in the form of the metastable  $\alpha$ ,  $\beta'$ , and  $\gamma$  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  $\beta$  form are preserved and cause the separation of  $\beta$  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 Haleblan 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

<i>P</i>	<i>F</i>
1	3
2	2
3	1
4	0

water. The formation of a compound produces a negative deviation from Raoult's law, and miscibility therefore increases as the temperature falls, as shown in Fig. 3.8.

The effect of temperature on miscibility is of use in the preparation of paraldehyde enemas, which usually consist of a solution of paraldehyde in normal saline. Cooling the mixture during preparation allows more rapid solution, and storage of the enema in a cool place is recommended. (N.B. Enemas should be warmed to body temperature before use.)

(c) *Systems Showing Upper and Lower CSTs.* The decrease in miscibility with increase in temperature in systems having a lower CST is not indefinite. Above a certain temperature, positive deviations from Raoult's law become important and miscibility starts to increase again with further rise in temperature. This behaviour produces a closed-phase diagram as shown in Fig. 3.9, which represents the nicotine-water system.

In some mixtures where an upper and lower CST are expected, these points are not, in fact, observed since a phase change by one of the components occurs before the relevant CST is reached. For example, the ether-water system is expected to exhibit a lower CST, but water freezes before the temperature is reached.

*The Effects of Added Substances on Critical Solution Temperatures*

It has already been stated that a CST is an invariant point at constant pressure. These temperatures are very sensitive to impurities or added substances. In general, the effects of additives may be summarised by Table 3.3.

The increase in miscibility of two liquids caused by the addition of a third substance is referred to as blending. This is made use of in the formulation of Solution of Cresol with Soap BP 1968, which contains 50 per cent cresol. Cresol is only partially miscible with water but the soap in this preparation decreases the upper CST and produces complete miscibility at ordinary temperatures.

3. IMMISCIBLE LIQUIDS

In a mixture containing two immiscible liquids each liquid exerts its own vapour pressure independently of the other. The total vapour pressure,  $p$ , is therefore equal to the sum of the separate vapour pressures of the pure compounds ( $p_A^0$  and  $p_B^0$ , respectively), i.e.

$$p = p_A^0 + p_B^0$$

Table 3.3  
The Effects of Additives on CST

Type of CST	Solubility of additive in each component	Effect on CST	Effect on miscibility
Upper	Approx. equally soluble in both components	Lowered	Increased
Upper	Readily soluble in one component but not in other	Raised	Decreased
Lower	Approx. equally soluble in both components	Raised	Increased
Lower	Readily soluble in one component but not in other	Lowered	Decreased

The application of the Phase Rule to the distillation of such a system, which involves two liquids in equilibrium with a vapour, shows that only one degree of freedom exists,

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

i.e. the boiling point is constant at constant pressure and is independent of the composition. Since the liquid mixture will boil when its total vapour pressure is equal to atmospheric pressure, it follows that the boiling point is lower than that of either pure component, even the one with the lowest boiling point. After one of the components has been completely removed by distillation the boiling point will rise to that of the remaining component.

The constant boiling mixture will produce a vapour in which the number of molecules of each component ( $n_A$  and  $n_B$ , respectively) is proportional to its vapour pressure if ideal behaviour occurs, i.e.

$$\frac{n_A}{n_B} = \frac{p_A^0}{p_B^0} \tag{3.5}$$

But

$$n_A = \frac{m_A}{M_A} \quad \text{and} \quad n_B = \frac{m_B}{M_B} \tag{3.6}$$

where  $m_A$  and  $m_B$  are the masses of each component in the vapour and  $M_A$  and  $M_B$  are their molecular weights, and from Eqns (3.5) and (3.6)

$$\frac{m_A}{M_A} \times \frac{M_B}{m_B} = \frac{p_A^0}{p_B^0}$$

$$\frac{m_A}{m_B} = \frac{p_A^0 M_A}{p_B^0 M_B} \tag{3.7}$$

### Measurement of Surface Tension

Three of the most common methods of measuring surface tension are described below, together with the relevant correction factors and practical precautions that must be taken into account to obtain accurate results. Details of other methods are given in the references cited in the Bibliography.

#### 1. THE CAPILLARY RISE METHOD

This is one of the most accurate methods and is based on the measurement of the height to which a liquid rises in a capillary tube. Equation (4.10), which is a rearranged form of Eqn (4.9) can be used for approximate determinations.

$$\gamma = \frac{h\rho g r}{2} \text{ newtons/metre} \quad (4.10)$$

For more accurate results certain modifications of this equation should be taken into account to allow for—

(a) a change in the value of the contact angle ( $\theta$ ) between the liquid and the walls of the tube from the zero value assumed in Eqn (4.10) to a finite value,

(b) the hydrostatic pressure exerted by the small volume of liquid contained in the meniscus above the point from which the height  $h$  is usually measured, and

(c) the difference in the density of the liquid ( $\rho^L$ ) inside the capillary tube and that of the vapour ( $\rho^V$ ) outside the tube.

The corrected equation is—

$$\gamma = \frac{\left(h + \frac{r}{3}\right)(\rho^L - \rho^V)gr}{2 \cos \theta} \text{ newtons/metre} \quad (4.11)$$

#### Experimental Precautions

- The outer vessel must have a large diameter compared with the capillary, otherwise  $p_C \neq p_D$ .
- The capillary tube should be uniform in diameter and it should be circular in cross-section. If this is not so, then corrections must be made for ellipticity.
- To obtain the lowest value for the contact angle ( $\theta$ ) it is better to allow the meniscus to fall to rest than to rise up the tube to an equilibrium position. In addition, it is useful if the capillary walls are thoroughly wetted by the liquid before beginning the measurement. This can be done by passing liquid vapour through the cooled capillary, or by evacuating the capillary just before filling.

(d) The difference in the height of the menisci should be measured with a cathetometer, preferably with two telescopes, and care is necessary in lighting and viewing the meniscus in the large vessel.

(e) Adequate temperature control is necessary.

#### 2. THE DROP WEIGHT METHOD

The mass,  $m$  kg, of an ideal drop of liquid having a surface tension  $\gamma$  newton/metre, falling from a tube of external radius  $r$  m, is given by Tate's equation (1864), Eqn (4.12),

$$mg = 2\pi r \gamma \text{ newtons} \quad (4.12)$$

where  $g$  is the gravitational constant ( $9.807 \text{ m/s}^2$ ). In practice, the drop that falls from a tube is not ideal since the drop is constricted at the point where the break occurs to a diameter less than that of the tip of the tube. In addition, only part of the liquid protruding from the tip actually breaks away, and this falls in the form of more than one drop.

Harkins and Brown (1919) introduced a correction factor which takes the shape of the drop into account, and Eqn (4.13) then becomes

$$mg = 2\pi r \gamma \cdot f\left(\frac{r}{V^{-3}}\right) \text{ newtons} \quad (4.13)$$

The correction factor  $f(r/V^{-3})$  is a function of the radius of the tip  $r$  and the cube root of the volume,  $V$ , of the drop. It is, in fact, the fraction of an ideal drop that actually falls, and Harkins and Brown give tables and graphs showing the value of their correction factor for various values of the actual ratio  $r/V^{-3}$ .

An error is often introduced by attempting to obtain 'relative' values of surface tension by comparing drop weights of two different liquids. The results can be used in this way only if the surface tensions and densities of the two liquids and the tips of the tubes are chosen so that the values of  $r/V^{-3}$  are within the narrow limits where the correction curve is approximately horizontal.

#### Experimental Precautions

- The tip should be sharply ground with no imperfections in the outer circumference.
- The drops should be allowed to form slowly, especially in the later stages, otherwise the weight of the drop is greater than expected due to the effects of liquid streaming into the drop during the final, relatively slow stages of detachment.
- Adequate temperature control is necessary.

# Contents

PREFACE PAGE ix

## Part One Physical Pharmaceutics

1 Units	3	5 Disperse systems	54
2 Solutions	7	6 Kinetics	89
3 Phase equilibria	17	7 Rheology	115
4 Surface and interfacial phenomena	33		

## Part Two Pharmaceutical Technology

8 Formulation and development	131	17 Size separation	192
9 Packaging	133	18 Mixing	200
10 Introduction to industrial processing	142	19 Powder flow and compaction	211
11 Fluid flow	146	20 Filtration	234
12 Heat transfer	149	21 Centrifugation	245
13 Mass transfer	162	22 Extraction	251
14 Evaporation	164	23 Distillation	262
15 Particle size	174	24 Drying	270
16 Size reduction	183	25 Materials of pharmaceutical plant construction	282

## Part Three Biological Pharmacy

26 Outline of the development of microbiology	289	31 Antiseptics, disinfectants and preservatives	353
27 Fundamentals of microbiology	298	32 Antibiotics	366
28 Bacteriological methods	317	33 Immunology	375
29 Dynamics of antimicrobial action	333	34 Blood and related products	414
30 Evaluation techniques in microbiology	341		

## Part Four Ligatures and Sutures

35 Surgical ligatures and sutures			429
-----------------------------------	--	--	-----

## Part Five Radioactive Isotopes

36 Radioactive isotopes			435
-------------------------	--	--	-----

## Appendix

Forces between molecules, ions and atoms			455
--	--	--	-----

INDEX PAGE 457