at a specific transition temperature. For example, sodium sulfate exists as the decahydrate $Na_2SO_4.10H_2O$ up to 32.5°C and its dissolution in water is an endothermic process. Its solubility therefore increases with a rise in temperature until 32.5 °C is reached. Above this temperature the solid is converted into the anhydrous form (Na_2SO_4) and the dissolution of this compound is exothermic. The solubility therefore exhibits a change from a positive to a negative slope as the temperature exceeds the transition value.

Molecular structure of solute. It should be appreciated from the previous comments in this chapter on the prediction of solubility that the nature of the solute and the solvent will be of paramount importance in determining the solubility of a solid in a liquid. It should also be realized that even a small change in the molecular structure of a compound can have a marked effect on its solubility in a given liquid. For example, the introduction of a hydrophilic hydroxyl group can produce a large improvement in water solubility as evidenced by the more than 100-fold difference in the solubility of phenol compared with benzene.

In addition, the conversion of a weak acid to its sodium salt leads to a much greater degree of ionic dissociation of the compound when it dissolves in water. The overall interaction between solute and solvent is increased markedly and the solubility consequently rises. An example of this effect is provided by a comparison of the aqueous solubility of salicylic acid and that of its sodium salt, which are 1 in 550 and 1 in 1, respectively.

The reduction in aqueous solubility of a parent drug by its esterification may also be cited as an example of the effects of changes in the chemical structure of the solute. Such a reduction in solubility may be beneficial to provide a suitable method for:

- masking the taste of a parent drug. For example, chloramphenicol palmitate has been used in paediatric suspensions rather than the more soluble and very bitter tasting chloramphenicol base
- protecting the parent drug from excessive degradation in the gut, e.g. erythromycin propionate is less soluble and consequently less readily degraded than erythromycin
- increasing the ease of absorption of drugs from the gastrointestinal tract, e.g. erythromycin propionate is also more readily absorbed than erythromycin.

Nature of solvent: cosolvents. The importance of the nature of the solvent has already been discussed in terms of the statement 'like dissolves like' and in relation to solubility parameters. In addition, the point has been made that mixtures of solvents may be employed. Such mixtures are often used in pharmaceutical practice in order to obtain aqueous-based systems that contain solutes in excess of their individual solubility in pure water. This is achieved by using cosolvents such as ethanol or propylene glycol, which are miscible with water and which act as better solvents for the solute in question.

For example, the aqueous solubility of metronidazole is about 100 mg in 10 mL. The solubility of this drug can be increased markedly by the incorporation of one or more water-miscible cosolvents so that a solution containing 500 mg in 10 mL (and thus suitable for parenteral administration in the treatment of anaerobic infections) can be obtained.

Crystal characteristics: polymorphism and solvation. When the conditions under which crystallization is allowed to occur are varied, some substances produce crystals in which the constituent molecules are aligned in different ways with respect to one another in the lattice structure. These different crystalline forms of the same substance, which are known as polymorphs, consequently possess different lattice energies and this difference is reflected by changes in other properties. For example, the polymorphic form with the lowest free energy will be the most stable and possess the highest melting point. Other less stable (or metastable) forms will tend to transform into the most stable one at rates that depend on the energy differences between the metastable and stable forms.

Many drugs exhibit polymorphism, e.g. steroid and sulfonamide polymorphs are common. Polymorphs are explained more fully in Chapters 8 and 23, which also includes an explanation of why polymorphs may have different solubilities. Examples of the importance of polymorphism with respect to the bioavailability of drugs are given in Chapter 20.

The effect of polymorphism on solubility is particularly important from a pharmaceutical point of view, because it provides a means of increasing the solubility of a crystalline material, and hence its rate of dissolution, by using a metastable polymorph.

Although the more soluble polymorphs are metastable and will convert to the stable form, the rate of such conversion is often slow enough for the