metastable form to be regarded as being *sufficiently stable* from a pharmaceutical point of view. The degree of conversion should obviously be monitored during storage of the drug product to ensure that its efficacy is not altered significantly. There are products on the market containing a more soluble, but less stable, polymorph of the drug, where the chosen polymorph is *stable enough* to survive the approved storage conditions and shelf-life.

Conversion to the less soluble and most stable polymorph may contribute to the growth of crystals in suspension formulations. Examples of the importance of polymorphism with respect to the occurrence of crystal growth in suspensions are given in Chapter 26.

The absence of a crystalline structure that is usually associated with an *amorphous* powder (discussed in Chapter 8) may also lead to an increase in the solubility of a drug when compared with that of its crystalline form.

In addition to the effect of polymorphism, the lattice structures of crystalline materials may be altered by the incorporation of molecules of the solvent from which crystallization occurred (discussed in Chapter 8). The resultant solids are called *solvates* and the phenomenon is referred to correctly as *solvation* and sometimes incorrectly and confusingly as *pseudopolymorphism*. The alteration in crystal structure that accompanies solvation will affect the internal energetics of the solid so that the solubility of the solvated and unsolvated crystals will differ.

If water is the solvating molecule, i.e. a *hydrate* is formed, then the interaction between the substance and water that occurs in the crystal phase reduces the amount of energy liberated when the solid hydrate dissolves in water. Consequently, hydrated crystals tend to exhibit a lower aqueous solubility than their unhydrated forms. This decrease in solubility can lead to precipitation of drugs from solutions.

In contrast, the aqueous solubility of other, i.e. non-aqueous, solvates is often greater than those of the unsolvated forms. Examples of the effects of solvation and the attendant changes in solubilities of drugs on their bioavailabilities are given in Chapter 20.

Particle size of the solid. The changes in interfacial free energy that accompany the dissolution of particles of varying sizes cause the solubility of a substance to increase with decreasing particle size, as indicated by Equation 2.10.

$$\log \frac{S}{S_0} = \frac{2\gamma M}{2.303RT\rho r} \tag{2.10}$$

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, 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.

The increase in solubility with decrease in particle size ceases when the particles have a very small radius (less than about 1 μm), and any further decrease in size can cause 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 particle size decreases. Such solubility changes are rarely a problem in conventional dosage forms and drug delivery but could be significant with nanotechnology products.

pH. If the pH of a solution of either a weakly acidic drug or a salt of such a drug is reduced,then the proportion of unionized acid molecules in the solution increases. Precipitation may occur, therefore, because the solubility of the unionized species is less than that of the ionized form. Conversely, in the case of solutions of weakly basic drugs or their salts, precipitation is favoured by an increase in pH. Such precipitation is an example of one type of chemical incompatibility that may be encountered in the formulation of liquid medicines.

This relationship between pH and solubility of ionized solutes is extremely important with respect to the ionization of weakly acidic and basic drugs as they pass through the gastrointestinal tract and can experience pH changes between about 1 and 8. This will affect the degree of ionization of the drug molecules which in turn influences their solubility and their ability to be absorbed. This aspect is discussed elsewhere in this book in some detail and the reader is referred in particular to Chapters 3 and 20.

The relationship between pH, pK_a and solubility of weakly acidic or weakly basic drugs is given by a modification of the Henderson–Hasselbalch equation. To avoid repetition here, the reader is referred to the relevant section of Chapter 3.

Common ion effect. The equilibrium in a saturated solution of a sparingly soluble salt in contact with undissolved solid may be represented by: