be crystallized by adding water to a near-saturated solution of the drug in ethanol.

The processes by which a crystal forms are called nucleation and growth. Nucleation is the formation of a small mass onto which a crystal can grow. Growth is the addition of more solute molecules onto the nucleation site. In order to achieve nucleation and growth, it is necessary to have a supersaturated solution. As mentioned above, a supersaturated solution is one where the amount of solute dissolved in the liquid is greater than the true solubility. Supersaturated solutions are not thermodynamically stable, so in these circumstances the system will adjust in order to move back to the true solubility, and to do this, the excess solute will precipitate. However, in some circumstances the process of nucleation can be slow. Many students will at some stage have had a supersaturated solution which has not crystallized but on simply scratching the side of the beaker with a glass rod, crystallization was induced. The scratching action produces a small amount of rough surface that acts as a nucleation site and causes the supersaturated solute to precipitate rapidly.

Polymorphism

If the crystallization conditions are changed in any way, it is possible that the molecules may start to form crystals with a different packing pattern to that which occurred when the original conditions were used. The change in conditions could be a different solvent, a change in the stirring, or different impurities being present. In Figure 8.1b, an alternative packing arrangement is shown to that which occurred for the same molecule in Figure 8.1a. As both the packing arrangements in Figure 8.1 are repeating ordered systems, they are both crystals; these would be called *polymorphic forms*.

By looking at the packing arrangements in Figure 8.1, it can be seen that the molecules in (a) are more spaced out than those in (b), which means that the two crystal forms would have different densities (i.e. the same mass of material would occupy different volumes). It looks as though it would be easier to physically pull a molecule off structure (a) than (b), as the molecules in (b) are more interwoven into the structure. If this were the case, then (a) would have a lower melting point than (b), and (a) may dissolve more easily. Also if an attempt were made to mill the two crystals, it looks like (a) would break easily, as there are natural break lines (either vertically or horizontally), whereas (b) does not seem to have an obvious weak line to allow easy breakage. This could mean that the milling and compaction (tableting) properties of the two forms will differ. In summary, a change in the packing arrangement of the same molecule, giving two different crystal forms, could result in significant changes in the properties of the solid.

Many organic molecules, including drugs and excipients, exhibit polymorphism. Often this is of a form called *monotropic polymorphism*, which means that only one polymorphic form is stable and any other polymorph that is formed will eventually convert to the stable form. However, some materials exhibit *enantropic polymorphism*, which means that under different conditions (temperature and pressure) the material can reversibly transform between alternative stable forms; this type of behaviour will not be considered further here. Considering monotropic polymorphism, the true stable form has the highest melting point and all other forms are described as metastable. This means that the other forms exist for a period of time, and thus appear stable, but given a chance they will convert to the true stable form. Different metastable forms can exist for very short times or many months before they convert to the stable form, depending upon the conditions under which they are stored.

In general, there will be a correlation between the melting point of the different polymorphs and the rate of dissolution, because the one with the lowest melting point will most easily give up molecules to dissolve, whereas the most stable form (highest melting point) will not give up molecules to the solvent so readily.

High melting point = strong lattice
= hard to remove a molecule
= low dissolution rate

Low melting point = weak lattice
= easy to remove a molecule
= high dissolution rate

It is relatively easy to understand that changes in polymorphic form can cause changes in the rate at which a drug will dissolve. However, it is less easy to understand why this can lead to a change in the apparent solubility. Nonetheless, it is true that when a metastable polymorphic form is dissolved, it can give a greater amount of material in solution than the saturated solubility. In other words, metastable forms can dissolve to give supersaturated solutions. These supersaturated solutions will eventually