the majority of drugs and excipients exist as solids, thus the study of solid-state properties is of enormous pharmaceutical importance.

Solid particles are made up of molecules that are held in close proximity to each other by intermolecular forces. The strength of interaction between two molecules is due to the individual atoms within the molecular structure. For example, hydrogen bonds occur due to an electrostatic attraction involving one hydrogen atom and one electronegative atom, such as oxygen. For molecules which cannot hydrogen bond, attraction is due to van der Waals forces. The term *van der Waals forces* is generally taken to include dipole-dipole (Keesom), dipole-induced dipole (Debye) and induced dipole-induced dipole (London) forces. In this context a dipole is where the molecule has a small imbalance of charge from one end to the other, making it behave like a small bar magnet. When the molecules pack together to form a solid, these dipoles align and give attraction between the positive pole of one and the negative pole on the next. Induced dipoles are where the free molecule does not have an imbalance of charge, but an imbalance is caused by bringing a second molecule into close proximity with the first.

## Crystallization

Materials in the solid state can be crystalline or amorphous (or a combination of both). Crystalline materials are those in which the molecules are packed in a defined order, and this same order repeats over and over again throughout the particle. In Figure 8.1a, an ordered packing of a molecule is shown; here the shape of the molecule is shown as a 'hockey stick' style image, which is representing a planar structure with a functional group pointing up at the end. This is not a real molecule – it has been drawn to provide an easy representation of a possible crystal packing arrangement. A characteristic property of a crystal is that it has a melting point. The melting point is the temperature at which the crystal lattice breaks down, due to the molecules having gained sufficient energy from the heating process to overcome the attractive forces that hold the crystal together. It follows that crystals with weak forces holding the molecules together (such as paraffins, which only have London van der Waals interactions) have low melting points, whereas crystals with strong lattices (i.e. those held together with strong attractive forces) have high melting points.

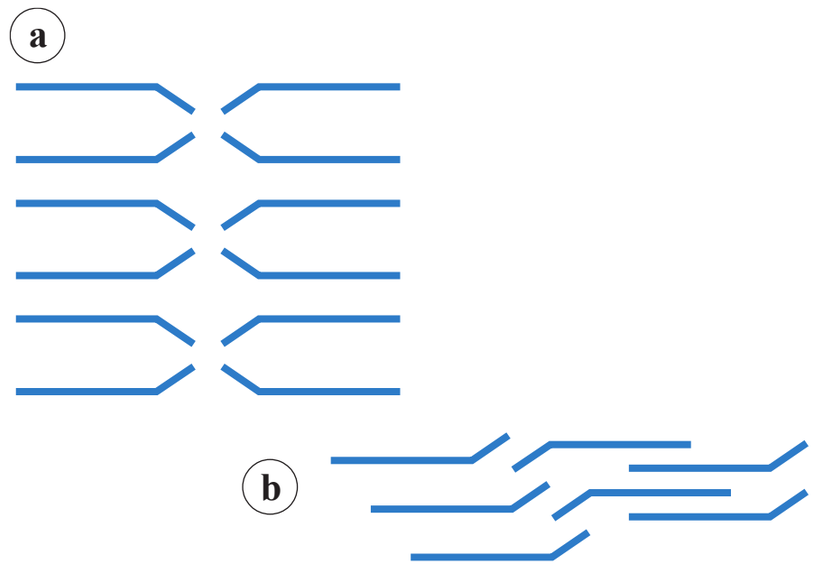


**Fig. 8.1** • A representation of two polymorphic forms of a crystal consisting of a molecule shown as a 'hockey stick' shape.

Crystals are produced by inducing a change from the liquid to the solid state. There are two options: one is to cool a molten sample to below the melting point. Pharmaceutical examples of crystallizing through cooling include the formation of suppositories, creams and semi-solid matrix oral dosage forms (although these will not always yield crystalline material). The other method of crystallization is to have a solution of the material and to change the system so that the solid is formed. At a given temperature and pressure, any *solute* (where the solute is the material that has been dissolved and the liquid is the *solvent*) has a certain maximum amount that can be dissolved in any liquid (called a *saturated solution*). If crystals are to be formed from a solution, it is necessary to have more solute present than can be dissolved, which is known as a *supersaturated solution*. As crystals form from a supersaturated solution, the systems will progress until there are solid particles in equilibrium with a saturated solution. In order to make a solid precipitate out of solution one can:

- remove the liquid by evaporation, thus making the concentration of solute rise in the remaining solvent (this is the way sea salt is prepared)
- cool the solution, as most materials become less soluble as the temperature is decreased
- add another liquid which will mix with the solution, but in which the solute has a low solubility. This second liquid is often called an *antisolvent*.

Many drugs are crystallized by adding water as an anti-solvent to a solution of the drug in an organic liquid. For example, if a drug is almost insoluble in water but freely soluble in ethanol, the drug could