In conclusion, the stable polymorphic form will have the slowest dissolution rate, so there may be occasions when it would be desirable to speed the dissolution by using a metastable form. However, the risk associated with using the metastable form is that it will convert back to the stable form during the product life, and give a consequent change in properties.

As polymorphism can have such serious consequences for bioavailability of drugs with low aqueous solubility, it is essential that manufacturers check for the existence of polymorphism and ensure that they use the same appropriate polymorphic form every time they make a product. New drugs are therefore screened to see how many polymorphs (and solvates and hydrates – see below) exist, and then to identify which one is the most stable. The screening process requires many crystallizations from numerous different solvent systems, with variations in method and conditions, in order to try to induce different polymorphs to form. The products are then checked with spectroscopy (e.g. Raman) and X-ray diffraction to see if they have different internal packing (see also Chapter 23). Sadly, there are examples of products being taken to market with what was believed to be the stable form, only for the stable form to be produced at a later stage. In these circumstances, the stable form may have been inhibited from being formed by a certain impurity, which may have been lost due to an alteration in the method of chemical synthesis of the drug, so the stable form suddenly was produced. Having produced the stable form, if the drug is poorly soluble it would be probable that the bioavailability would reduce. Also, having made the stable form, it is often then very hard to stabilize the metastable form again. This can result in products having to be recalled from the market and reformulated and retested clinically. The fact that major pharmaceutical companies, all of whom take the study of physical form very seriously, have seen the stable form arrive after product launch shows that it is difficult to be sure that you are working with the most stable form of the drug.

As was mentioned above, many properties other than rate of solution can change when a material is in a different polymorphic form. For example, paracetamol is a high-dose drug with poor compression properties, which can make it difficult to form into tablets. This is because there is an upper limit on the size of tablet that can be swallowed easily, so for high-dose drugs the amount of compressible excipient that can be added is modest. Consequently, researchers have tried to experiment with different polymorphic forms of paracetamol in order to find one that is more compressible.

Hydrates and solvates

It is possible for materials to crystallize and in so doing to trap individual molecules of the solvent within the lattice. If the solvent used is water, the material will be described as a *hydrate*. This entrapment is often in an exact molar ratio with the crystallizing material; for example, a monohydrate will have one molecule of water for each molecule of the crystallizing material. It is possible to have different levels of hydrate; for example, some drugs can exist as a monohydrate, dihydrate and trihydrate (respectively one, two and three molecules of water to each molecule of drug). Morris (1999) notes that about 11% (over 16 000 compounds) of all structures recorded on the Cambridge Structural Database exist as hydrates. Of the classes of hydrate materials that were similar to drugs, about 50% were monohydrates, over 20% were dihydrates, 8% were trihydrates and 8% were hemihydrates (1 water molecule:2 host); other hydrate levels (up to 10 water:1 host) became progressively less common.

If solvents other than water are present in a crystal lattice, the material is called a *solvate*. For example, if ethanol is present it would be an ethanolate. In general, it is undesirable to use solvates for pharmaceuticals as the presence of retained organic material would be regarded as an unnecessary impurity in the product, unless it was seen to possess advantageous properties and be safe for pharmaceutical use. If the organic solvent were toxic in any way it would obviously be inappropriate for pharmaceuticals. For this reason discussion will be limited to hydrates.

Hydrates often have very different properties from the anhydrous form, in the same way as two different polymorphs have different properties from each other. For this reason, the difference between hydrates and anhydrous forms is sometimes described inelegantly as *pseudopolymorphism*. With polymorphism, the stable form will have the highest melting point and the slowest dissolution rate (see above). However, with hydrates it is possible for the hydrate form to have either a faster or slower dissolution rate than the anhydrous form. The most usual situation is for the anhydrous form to have a faster dissolution rate than the hydrate; an example