a constant temperature. TGA thus allows determination of water content *after* exposure of a sample to humidity, while DVS records the change in weight of a sample *during* exposure to humidity.

# Physical form

The solid-state is probably the most important state when considering development of a drug candidate into a drug product (discussed further in Chapter 8). Many solid-state (or physical) forms may be available and each will have different physicochemical properties (including solubility, dissolution rate, surface energy, crystal habit, strength, flowability and compressibility). In addition, physical forms are patentable, so knowing all of the available forms of a drug candidate is essential both in terms of optimizing final product performance but also in ensuring market exclusivity.

## Polymorphism

When a compound can crystallize to more than one unit cell (i.e. the molecules in the unit cells are arranged in different patterns) it is said to be *polymorphic* (Chapter 8). The form with the highest melting temperature (and by definition the lowest volume) is called the *stable* polymorphic form and all other forms are *metastable*. Different polymorphs have different physicochemical properties, so it is important to select the best form for development. A defining characteristic of the stable form is that it is the only form that can be considered to be at a thermodynamic position of equilibrium (which means that over time all metastable forms will eventually convert to the stable form). It is tempting therefore to consider formulating only the stable polymorph of a drug, since this ensures there can be no change in polymorph upon storage. The stable form might, however, have the worst processability (for instance, the stable form I of paracetamol has poor compressibility, while the metastable form II has good compressibility), or lowest bioavailability (for instance, the presence of the B or C forms of chloramphenicol palmitate dramatically reduces bioavailability). Selection of polymorphic form is not necessarily straightforward although if the stable polymorph shows acceptable bioavailability then it is of course the best option for development.

## Polymorphism screening

Polymorph screening at the preformulation stage is performed in much the same manner as described earlier for salt screening. Basic screening is achieved by crystallizing the drug candidate from a number of solvent or solvent mixtures of varying polarity. A small amount of drug (around 0.5 mg) is added into each well of a 96-well plate. To each well is added a small volume of each solvent or solvent mixture. After an appropriate length of time, the presence in each well of crystals is checked with an optical device (for instance a microscope or a nephelometer), using the strategies described previously for salt screening to facilitate crystallization.

X-ray powder diffraction (XRPD) provides structural data to identify and differentiate polymorphs. Figure 23.13 shows the powder diffractograms for two polymorphs of sulfapyridine; it is immediately apparent that each has a unique set of intensity peaks and so the forms are qualitatively different. The $2\theta$ angles for each peak provide a 'fingerprint' for each form, while the intensities of each peak can be used as the basis for a quantitative assay for each form.

Differential scanning calorimetry (DSC) data differentiate polymorphs on the basis of their melting points and heats of fusion, thus providing thermodynamic information. This means DSC can identify which polymorph is stable and which are metastable. In addition, the heat of fusion can be used to calculate ideal solubility. Assuming there is only one polymorph present in a sample, and that it is the stable form, heating the sample in the DSC should

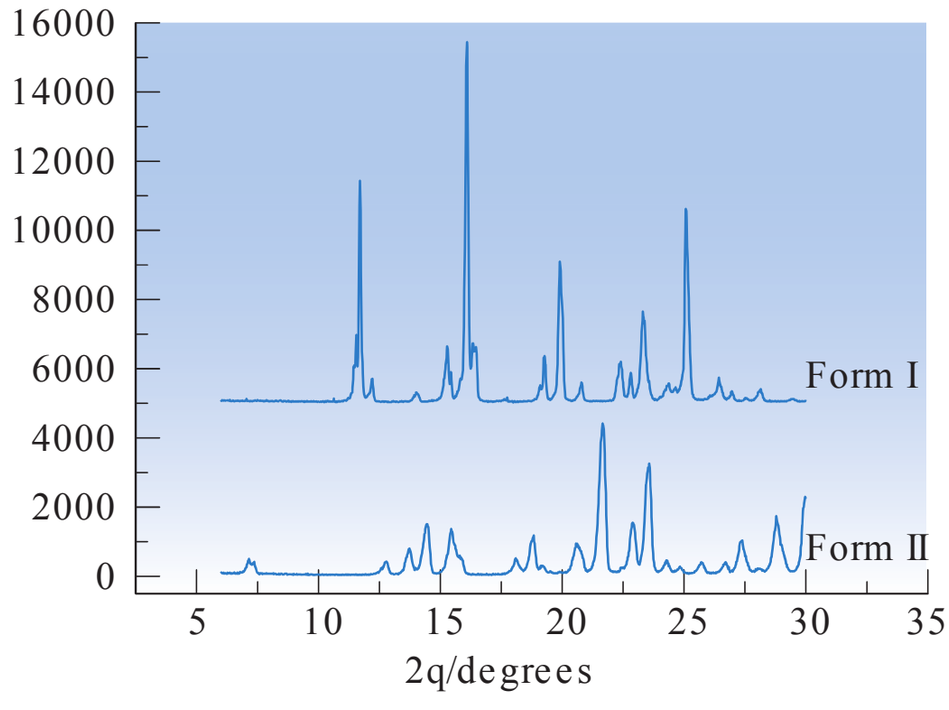


**Fig. 23.13** • XRPD diffractograms for two polymorphs of sulfapyridine.