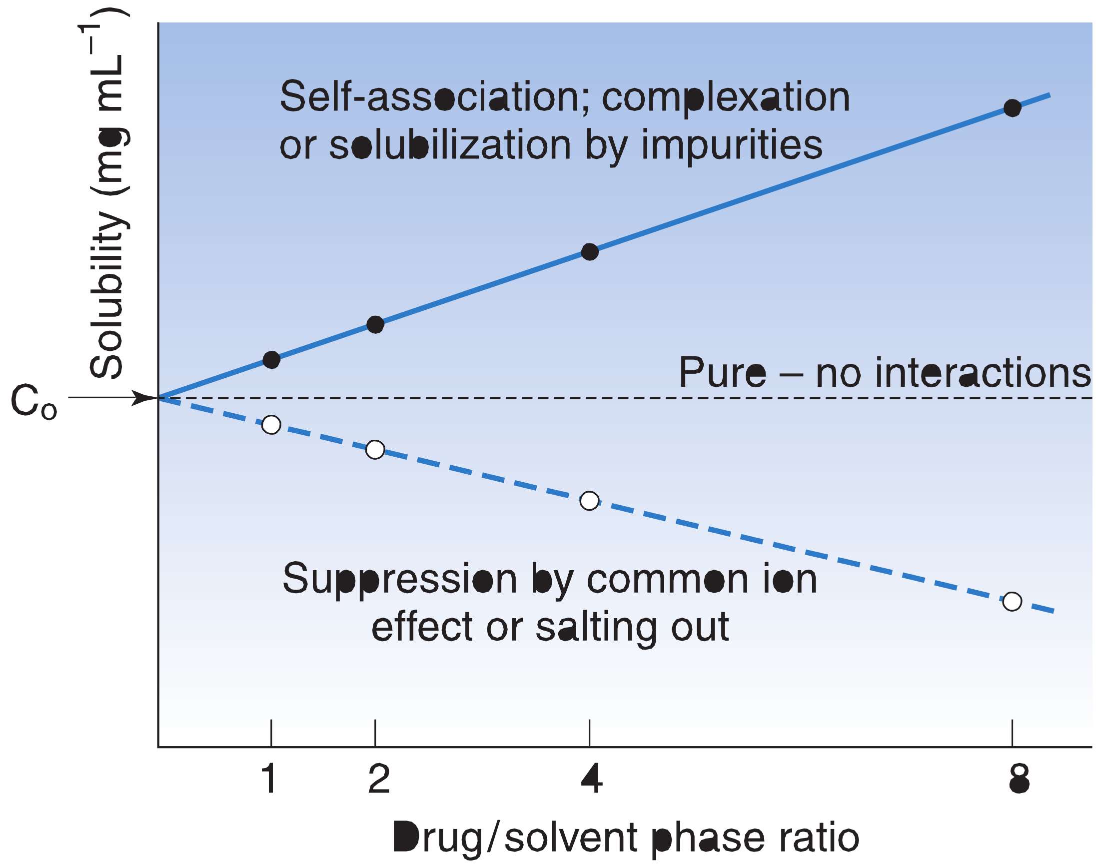

Fig. 23.7 • Effect of drug:solvent ratio when the drug is impure.

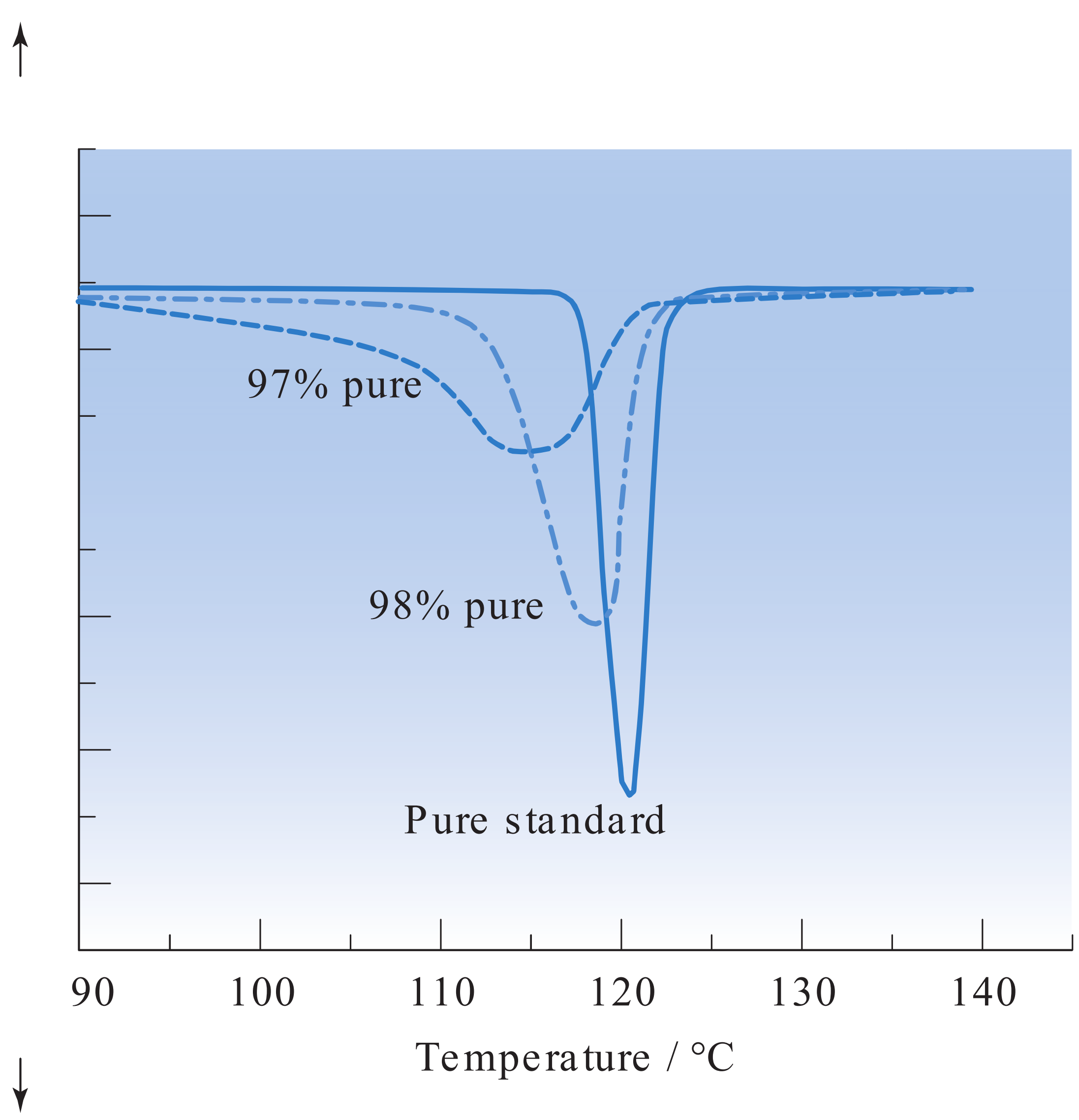

Fig. 23.8 • DSC thermal traces for benzoic acid of varying purity.

of a material. Qualitatively, if the melting endotherm recorded using DSC is very broad, then the sample is likely to be impure (see Fig. 23.8).

If the melting point and heat of fusion of the pure drug are known, then the purity of an impure sample can be quantified by analysis of DSC data. Analysis requires determination of the fraction of sample melted as a function of temperature. This is easily achieved by recognizing that integration of the peak area of melting gives the total heat of melting (Q). Partial integration of the melting endotherm to any particular temperature must therefore give a smaller heat (q). The fraction of material melted at any temperature (F_T) is then:

$$F_T = \frac{q}{Q} \tag{23.8}$$

Changes in F_T values as a function of temperature are easily measured. The van't Hoff equation (Eqn 23.9) predicts that a plot of $\frac{1}{F_T}$ versus temperature should be a straight line of slope $\frac{-RT_m^2 x_2}{\Delta H}$, from which the mole fraction of the impurity (x_2) can be calculated.

$$T = T_m - \frac{RT_m^2 x_2}{\Delta H} \cdot \frac{1}{F_T} \tag{23.9}$$

Molecular dissociation

Approximately two-thirds of marketed drugs ionize between pH 2 and 12 (analysis of the 1999 World Drug Index by Manallack, 2007). Understanding acid and base behaviour is thus extremely important, not only because of the number of ionizable drugs available, but also because the solubility of an acidic or basic drug will be pH-dependent (and because possession of an ionizable group opens the possibility of solubility manipulation via salt formation). Determining the pK_a of a drug is the next step in preformulation characterization. This is particularly important with drugs intended for peroral administration as they will experience a range of pH environments, and it is important to know how their degree of ionization may change during passage along the gastrointestinal tract.

The principles of acid-base equilibria are discussed in Chapter 3, where the Henderson-Hasselbalch equations (Eqns 3.15 and 3.19) were derived for acid and base species.

The Henderson-Hasselbalch equations allow calculation of the extent of ionization of a drug as a function of pH, if the pK_a is known. When the pH is significantly below the pK_a (by at least 2 pH units), a weakly acidic drug will be completely unionized and when the pH is significantly above the pK_a (by at least 2 pH units) a weakly acidic drug