

(Jozwiakowski et al., 1993; Carstensen and Franchini, 1995). In the latter case, amiloride HCl dihydrate polymorphs A and B showed statistically insignificant differences in solubility over the temperature range of 5°C–45°C in 0.15% NaCl. Given the wide range of behaviors of various drugs, solubility differences between solid phases should be determined experimentally early in the drug development process to identify any potentially useful forms.

Higuchi et al. (1963), in the study of methylprednisolone polymorphs, noted that the ratio of solubility between polymorphs should remain constant regardless of the solvent. This holds true as long as Henry's Law is obeyed, since solvent-dependent terms are cancelled when the temperature dependence of the solubilities is expressed as a ratio. Their resultant expression shows that, when the activity coefficients are 1.0 (dilute solution), the solubility ratio (S_1/S_2) depends only on the enthalpy change for the transition ($\Delta H_{1,2}$), the gas constant (R), and the temperature (T):

$$\frac{d \ln(S_1/S_2)}{dT} = \frac{\Delta H_{1,2}}{RT^2} \quad (19.4)$$

The magnitudes of the solubility of forms I and II of this drug varied significantly in water, decyl alcohol, and dodecyl alcohol. However, their data showed that the solubility ratio was independent of solvent, but dependent on temperature. Figure 19.3 shows the data for these polymorphs in water. The difference in slopes (indicating a difference in enthalpies of fusion) for the two polymorphs can be used to calculate a transition temperature, where both forms have the same physical stability. The identity of the metastable form and the degree of solubility enhancement both depend on the temperature chosen for comparison.

This constancy of solubility ratio between solvents for two polymorphs at a given temperature does not apply to solvated/nonsolvated pairs, where additional terms arising from the release of the solvate complicate the calculations.

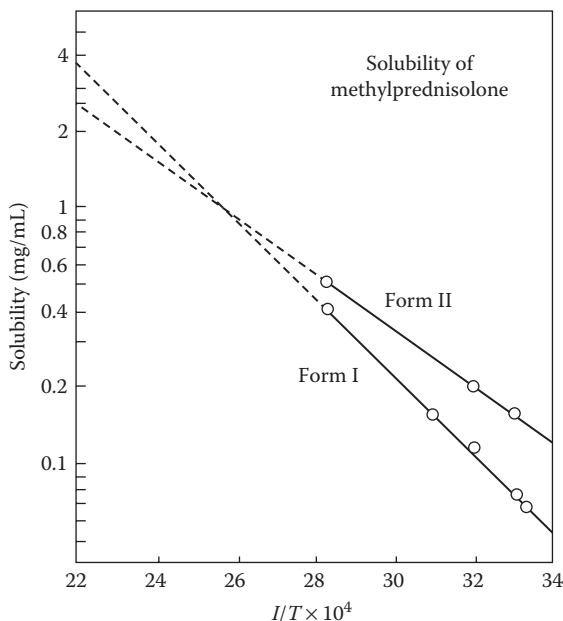


FIGURE 19.3 Water solubility of methylprednisolone polymorphs versus temperature. (Reproduced from Higuchi, W. I. et al. *J. Pharm. Sci.*, 52, 150–153, 1963. With permission from American Pharmaceutical Association.)