5.2 Release

Drug absorption depends on the release of the drug substance from the drug product (dissolution), the solubility, and the permeability across the gastrointestinal (GI) tract. The release characteristics of a drug delivery system are often determined by the manufacture of the product and highly affected by drug solubility, which also affects dissolution rates. The release step is followed by dissolution of the active ingredient. Dissolution of a pure substance follows the classic Noyes–Whitney equation:

$$dc/dt = kS(Cs - Ct) \tag{5.1}$$

where dc/dt is the rate of dissolution, k is the dissolution rate constant, S is the surface area of the dissolving solid, Cs is the saturation concentration of drug in the diffusion layer, and Ct is the concentration of drug in dissolution media (or the bulk).

This equation is of great value in the formulation studies, wherein increase in the surface area of aggregates is the most powerful tool to optimize dissolution. The innate property in the equation that is subject to much of preformulation work refers to the solubility of the compound. In dissolution theory, it is assumed that an aqueous diffusion layer or stagnant liquid film of thickness h exists at the surface of a solid undergoing dissolution, as observed in Figure 5.1. This thickness h represents a stationary layer of solvent in which the solute molecules exist in concentrations from Cs to C. Beyond the static diffusion layer, at x greater than h, mixing occurs in the solution, and the drug is found at a uniform concentration, C, throughout the bulk phase (Figure 5.1).

The diffusion layer model of dissolution assumes that the dissolution of drug at the solid–liquid interface into a concentrated layer surrounding the solid particle is more rapid than the diffusion of dissolved drug from that layer into the bulk solution. This diffusion is therefore rate-limiting in observed dissolution. As diffusion involves kinetic energy, it is highly dependent on the temperature. For an ideal solution, no heat is absorbed or given off on dissolution; however, for a real solution, the heat of the solution (ΔH) can be either negative (heat is given off) or positive (heat is absorbed). The mathematical relationship of solubility (Cs) to temperature is:

$$\log Cs = (-\Delta H/2.303\ RT) + \text{constant} \tag{5.2}$$

where R is the gas constant and T is the absolute temperature. A plot of log Cs versus $1/T$ gives the value of the constant. A heat effect depends on whether the material

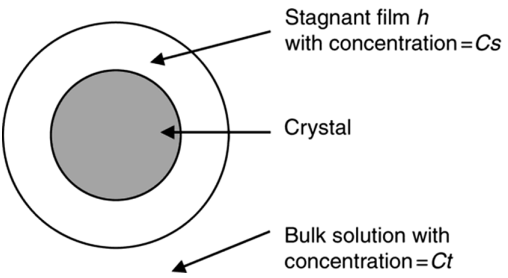

FIGURE 5.1 Diffusion layer model of dissolution.