common solid–air interfaces (Zografi et al., 1990). Equation 17.28 can be expressed in terms of the molar volume, V_m, of the solute:

$$\ln\left(\frac{S_{r1}}{S_{r2}}\right)=\left(\frac{2V_m\gamma}{RT}\right)\left(\frac{r_2-r_1}{r_1r_2}\right) \tag{17.29}$$

The above-described systems are by definition metastable and are affected by temperature fluctuations. Two other factors influencing solubility are the effect of change in crystal morphology and the creation of a higher-energy surface on particles by mechanical stress (grinding).

CRYSTAL GROWTH

Following a size reduction procedure, it is critical that the size is retained during the shelf life of the product; otherwise, the beneficial attributes associated with size reduction will not be realized. Therefore, an understanding of crystal growth phenomena is critical to successful pharmaceutical formulation.

Drug crystals grow via phase transition of a liquid or semisolid material into a solid crystalline form. This process can be described as three discrete steps:

1. Achievement of supersaturation
2. Formation of crystal nuclei
3. Crystal growth

In the context of this chapter, our interest lies in step 3. This section consists of a brief description of the first two steps, followed by a more in-depth treatment of crystal growth.

Supersaturation

The term *supersaturate* was coined in 1788 and was defined as *to add to a solution beyond saturation*. The state of supersaturation may be obtained through cooling, evaporation, or as a result of a chemical reaction between two homogeneous phases. In addition, in the case of drug solutions, supersaturation may be reached through dissolution of

1. A metastable and more thermodynamically energetic polymorph of the drug
2. An amorphous form of the drug
3. Crystals rendered metastable through mechanical means, which increase the surface free energy

The definition of supersaturation is as follows:

$$\sigma=\left(\frac{c_t-c_s}{c_s}\right) \tag{17.30}$$

where σ is the degree of supersaturation.

Although a supersaturated system may remain in this state for an appreciable length of time, it will eventually reach thermodynamic equilibrium through crystallization of excess solute.

Nucleation

This phenomenon is not fully understood; however, it may be described as the formation of minute particles of the solute, which act as nuclei for further deposition of the solute from a supersaturated