

SOLUBILITY

The aqueous solubility of APIs plays a central role in drug formulation. If the given drug substance is sufficiently soluble in water and stable in solution, formulation should proceed in a straightforward fashion. However, if the drug substance is insoluble or sparingly soluble in aqueous medium, this presents a much more difficult challenge in formulation development. The formulator may have to resort to addition of solubilizing agents or organic cosolvents. Particle size also affects the solubility of the compound itself since the free energy of the system increases with decreasing particle size.

The specific surface, which is defined as the surface divided by volume, increases dramatically with decreasing particle size. Figure 17.3 shows the specific surface of spherical particles as a function of diameter. Solubility is defined as the capacity of two or more substances to form spontaneously, one with the other, without chemical reaction, a homogeneous solution (Mader, 1971). One can further classify solubility into *macroscopic* and *microscopic* solubility (Braun, 1983). These two terms are discussed in the following. Note that the solubility of a solute in solvent at equilibrium is independent of particle size *except* for colloidal systems, which are nonequilibrium systems.

Macroscopic Solubility

Macroscopic solubility can be thought of as the usual thermodynamic solubility behavior of dispersions of particles down to a few micrometer in size. A broad definition of solubility was given earlier. Of more interest to us is a more restricted definition for solubility, which refers to the saturation concentration of solutions, that is, the maximum ratio of dissolved matter to solvent under given conditions. An important consideration in terms of thermodynamics is the link between solubility of a solid and the term phase, a phase by Gibbs' definition being a part of a system that is physically and chemically homogeneous in itself. According to Gibbs, the term phase only applies to situations where the number of interfacial molecules is negligible with respect to the number of bulk molecules, that is, if the interfacial energy is negligible compared with the chemical potential of the bulk such that $\gamma_S = \gamma_L$ in mixed phase.

Microscopic Solubility

Microscopic solubility refers to the *solubility* of colloidal systems, which is not strictly defined and depends on many factors. In colloidal systems, the number of interfacial molecules is not negligible with respect to the number of bulk molecules. This attribute is the basis for the special

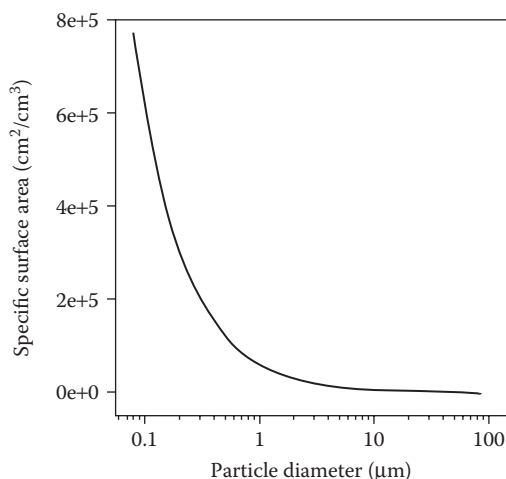


FIGURE 17.3 Specific surface area as a function of particle size.