attain the desired absorption and PK profile. This is a clear point of concern in developing a MR product for poorly water-soluble drugs.

Several known mechanism-based approaches, such as dissolution-controlled, diffusion- and/or erosion-controlled, combination of dissolution- and diffusion-controlled, and osmotically controlled systems have been widely used for sustained- or controlled-release delivery of water-soluble compounds. These models, in principle, are also applicable for designing MR delivery systems of water-insoluble drugs in combination with solubility-enhancing technology.

There have been a number of formulation approaches explored and widely practiced in the pharmaceutical industry to improve delivery of poorly water-soluble compounds, especially in development of immediate release dosage forms. These delivery approaches are based on various techniques described as following:

- Increased saturation solubility and as a consequence of the Noyes–Whitney equation (Equation 22.7), dissolution rate of the drug
- Particle size reduction (micronization and nanosization)
- Solid dispersion or solid solution
- Formation of the salt and polymorphs
- Use of co-solvents
- Complexation with the excipients such as cyclodextrins
- Other delivery techniques
- Achieving a sustained solubilization of the drug by
- Use of lipid-based delivery systems
- Use of surfactants to form micelles
- Other techniques

Drug solubilization and the ability to maintain the drug in solution throughout the GI tract, in particular at the site of absorption, become two of the important criteria when a specific, controlled- or sustained-release dosage form is being considered for delivery of a poorly water-soluble drug. Another important feature for such a delivery system is the ability to simultaneously release both drug and solubilization agent(s) throughout the GI tract.

Dissolution-Controlled Systems

For water-insoluble drugs, dissolution-controlled systems are an obvious choice for achieving sustained-release because of their slow dissolution rate characteristics. Theoretically, the dissolution process at steady state can be described by the Noyes–Whitney equation as shown in Equation 22.7. The rate of dissolution of a compound is a function of surface area, saturation solubility, and diffusion layer thickness. Therefore, the rate of drug release can be manipulated by changing these parameter.

$$\frac{dC}{dt} = \frac{D \times A(C_s - C_t)}{h \times V} \tag{22.7}$$

where dC/dt is the dissolution rate; D is the diffusion coefficient; A is the surface area of drug; C_s is the saturation solubility of the drug; C_t is the concentration at time, t; h the diffusion layer thickness; and V is the volume.

In recent years, nanotechnologies have received a great deal of attention in solving delivery problems of water-insoluble compounds. NanoCrystal® (Elan Drug Delivery, Inc., King of Prussia, PA) dispersions are small crystals of the drug substance, characterized in the submicron domain and often less than 400 nm in diameter. These dispersions are produced by high-energy wet milling (Elan Pharmaceutical 2004) and stabilized against agglomeration through surface adsorption of stabilizers, and have been incorporated into oral dosage forms to produce sustained-release profiles.