Alternatively, nanosized drug delivery particles, such as lipid-based nanoparticles or the nanostructured lipid dispersions, can be produced by dispersing water-insoluble drug in lipid-based excipients to form micron or submicron particles by high-pressure homogenization, microprecipitation, or dispersed-phase technology. In these cases, the drug release can be modified by proper selection of the solubility-enabling carrier(s) and controlling particle size of the final product (Elan Pharmaceutical 2004; Saffie-Siebert et al. 2005). Fine particles, for example, of the poorly water-soluble compounds cholesterol acetate (CA), GF, and megestrol acetate (MA) were produced by extraction of the internal phase of oil-in-water emulsions using supercritical carbon dioxide. Using the supercritical fluid extraction method, particles with mean volume diameter measured by light scattering technique ranging between 100 and 1000 nm were consistently produced. The study showed that emulsion droplet size, drug solution concentration, and organic solvent content in the emulsion were the major parameters responsible for particle size control. The GF and MA nanoparticles produced were crystalline as demonstrated by X-ray powder diffraction and exhibited a 5- to 10-fold increase in the dissolution rate compared with that of micronized powders. Theoretical calculations indicated that dissolution was governed mainly by the surface kinetic coefficient and the specific surface area of the particles produced. The rate of drug release could be manipulated and modified by formation of nanostructured particles by proper control of the particle size.

Diffusion- and Erosion-Controlled Systems

A diffusion-controlled system is typically based on the drug diffusion through an inert membrane or a drug-carrying matrix. Sustained- or controlled-release of water-insoluble drugs is achieved by a matrix diffusional system, in which the drug is homogeneously dissolved or dispersed throughout a matrix with addition of solubility-enhancing excipients such as lipids, surfactants, and/or a counterion for ionizable drugs. The physical form of the drug-carrying matrix may be a liquid, semisolid, or solid, and the finished dosage form may be a soft or hard gelatin capsule, or a tablet.

Matrix System

In a typical diffusion-controlled matrix system, drug in the outside layer of the matrix is exposed to the solution medium and dissolved first; it then diffuses out of the matrix as illustrated in Figure 22.2. The process continues at the interface between the bulk medium and solute and gradually moves toward the interior. In this approach, the dissolution rate of the drug within the matrix must be significantly faster than the diffusion rate of the dissolved drug. The release rate of a drug

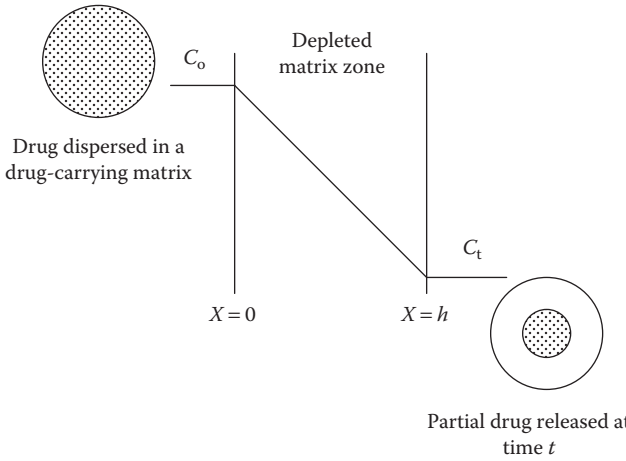

FIGURE 22.2 Schematic illustration of a diffusion-controlled matrix system for which the diffusion process is typically governed by Fick's Law (Equation 22.9).