1. SUSTAINED-RELEASE DRUG DELIVERY

Sustained-release drug delivery systems, which meter out the encapsulated drug over a long period of time, augment the effectiveness of therapy in several ways. An ideal sustained-release drug delivery system prolongs the half-life of the drug while maintaining the concentration of the released drug in the therapeutic range during the entire duration of drug release (Fig. 1). For cell-cycle phase-specific drugs in particular, prolonging the half-life of the administered drug has a profound effect on its efficacy by increasing the area under the “exposure vs time” curve for a given amount of drug while, at the same time, decreasing toxicity by reducing the high concentration peak of drug which otherwise occurs immediately after injection. Tissue distribution of the drug is often altered, resulting in higher concentrations and greater efficacy at the desired site, and lower exposure and toxicity elsewhere. Sustained-release formulations are an effective tool in cases where patient compliance is a problem. The feasibility of delivering treatment with fewer injections may enable outpatient treatment that can markedly improve the patient’s quality of life. There are, of course, economic incentives. For parenteral products that require administration and monitoring by medical personnel, decreasing the number of injections may reduce overall treatment cost. Proprietary sustained-release formulations can extend the economic viability of a compound beyond the termination of its patent life.

2. DEPOFOAM TECHNOLOGY

The DepoFoam® drug delivery system was developed to permit sustained release of drugs from a depot after direct injection into a body compartment or a tissue. The
Fig. 1. Schematic illustrating the objective of an ideal sustained-release drug delivery system.

DepoFoam particles are made up of synthetic cognates of lipids that occur naturally in the human body, such as phospholipids, cholesterol, and triglycerides. Unlike many types of microspheres, there are no foreign chemical entities in DepoFoam, and the delivery system itself completely disintegrates over time. When the particles are suspended in physiologic saline, the final product has the appearance and consistency of skim milk. During storage at 4–8°C, the drug remains inside the chambers of the DepoFoam particle. However, when the particle is injected into the patient, gradual reorganization of the structure of the particle occurs with the intermittent rupture of individual chambers and the sequential release of increments of drug. The duration of release can be up to 6–8 wk, which is a significantly longer duration than that obtained with current commercial lipid-based delivery systems. Appropriate injection routes include subcutaneous (sc), intramuscular (im), intrathecal, intraarticular, intraocular, intraperitoneal (ip), intrapleural, and epidural injections. The name DepoFoam reflects the foam-like appearance of the particles comprising the delivery system and the fact that, upon injection, they act as a depot for releasing the drug over time. DepoFoam particles are also known, as shown in the literature cited in this chapter, as multivesicular liposomes or multivesicular lipid particles. The technology is versatile, in that both small organic molecules and large macromolecules such as proteins and nucleic acids can be encapsulated in and released from DepoFoam particles.

2.1. Structure

Structurally, DepoFoam particles consist of microscopic spherical particles (average diameter 10–20 μm) composed of nonconcentric chambers, each separated from adjacent chambers by a bilayer lipid membrane (1,2). In contrast to unilamellar vesicles with a single spherical membranous shell, or multilamellar vesicles with multiple concentric membranes arranged like the layers of an onion, the lipids of a multivesicular liposome particle are arranged in a structure possessing hundreds of contiguous nonconcentric chambers (Fig. 2). Each chamber sequesters a small amount of the drug to be delivered. The individual internal compartments within a DepoFoam particle are typically on the order of a micron in diameter, whereas the diameter of the particle as a whole is on the order of tens of microns. The characteristic nonconcentric nature of a DepoFoam particle results in a higher aqueous-to-lipid ratio than for a concentric struc-