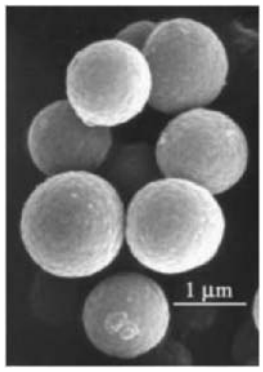

Figure 9-8 Example of physical appearance of microspheres. *Source*: Courtesy of Dr. Larry Brown, Baxter Healthcare Corporation.

degradation reactions include aggregation that often occurs with neutral liposomes of large size, promoted by trace elements and sedimentation and fusion where there occurs irreversible formation of larger vesicles promoted by high-stress curvature of small vesicles.

Liposomes are manufactured like other dispersed systems where compatible systems are compounded and sterile filtered, then combined and appropriately mixed by high shear techniques.

The Food and Drug Administration has published a guidance document worth reviewing on the chemistry, manufacturing, and controls for liposome drug products submitted in new drug applications (28).

MICROSPHERES

Microspheres have already been described in chapter 3, but since they are dispersed systems, some redundancy will occur here. Microspheres are solid, spherical particles, 1 to 1000 μm, usually polymeric formulations (Fig. 9-8). They are formulated primarily to sustain the release of drugs at the site of injection and have become popular controlled-release drug delivery systems. They also can be formulated to deliver a drug to a specific target and improve the safety profile of the drug. Microspheres serve as adjuvants for vaccines.

The most common polymer choice for microsphere formulations are the copolymers of lactic acid and glycolic acid (poly-lactic-co-glycolic acid; PLGA). Different levels and viscosities of the two polymers affect the rate of degradation and nature of erosion of the microsphere. Polyanhydride is another example of a microsphere polymer that gradually erodes. Other examples and discussion of microsphere formulations were covered in chapter 3.

Microspheres can be manufactured by a variety of techniques, summarized in Table 9-10.

Table 9-10 Microsphere Manufacturing Methods

1. Coacervation
   - Mix two immiscible liquids (concentrated polymer phase and a dilute liquid phase)
   - Alter conditions to favor polymer–polymer interactions, dehydration of polymer, and cross-linking
   - Polymer spheres will form around any material present
2. Divalent ion gelling
   - Form gel by mixing polymer with a divalent ion to cause cross-linking
   - An example is mixing of alginate with calcium chloride solution
3. Spray drying
4. Solvent evaporation
5. Precipitation
6. Freeze-drying
   - Organic, continuous phase sublimated at low temperature
   - Followed by sublimation of dispersed phase solvent
7. Supercritical fluid precipitation