7.6 Suspensions

When the lead compound has limited solubility and the efforts to enhance it fail and when there is a tendency for fast crystallization from solutions, or even when chemical stability is a problem, often formulating suspension dosage forms obviates some of these drawbacks. However, suspensions, by nature, must have higher viscosity to prevent the settling of particles and thus create problems in pourability, syringability, and so on. Appropriate selection of a vehicle that provides an ideal compromise among all characteristics thus becomes a critical factor, because the intent is to have as little solubility in the vehicle as possible to prevent crystallization from the solution that surrounds the suspended particles. As a result, weak acids and bases appear as poor choices for suspension formulation. In some instances, it may be possible to prepare a derivative with larger hydrophobic groups or salt formation that would have lower solubility, if preparing a suspension dosage form was particularly desired. Compounds that can form hydrates when in suspension state can create stability problems. A significant thermodynamic problem in suspension formulation comes from Ostwald ripening and crystal growth, not because of phase change but as a result of the differences in the solubility as a function of crystal size:

$$\frac{RT}{M} \ln\left(\frac{S_2}{S_1}\right) = \frac{2\sigma}{\rho}\left(\frac{1}{r_1} - \frac{1}{r_2}\right) \tag{7.23}$$

where R is the gas constant, T is the absolute temperature, S_1 and S_2 are the solubilities of crystals of radii r_1 and r_2, respectively, σ is the specific surface energy, ρ is the density, and M is the MW of the solute molecules. Temperature fluctuation is obviously one factor that promotes Ostwald ripening. Although phase changes can be studied using standard techniques, such as DSC, hot-stage microscopy, and XRPD, Ostwald ripening is best studied using microscopic methods. The art of suspension formulation is complex, as a large number of factors, including additives, can have a significant influence on the crystal growth; for example, dye molecules often attach to high-energy points on crystals, affecting their growth. Similarly, it is reported that polyvinyl pyrrolidine (PVP), a common ingredient of many suspension formulations, inhibits crystal growth. Albumin is also known to have a similar impact. The choice of additives is also governed by the final form of suspension. If it has to be sterilized, the additives must be able to sustain autoclave temperatures; besides, autoclaving can affect both the physical and chemical stabilities of the drug. Zeta potential measurements of suspensions often prove useful.

Shelf-life specifications of a suspension dosage form include redispersability on storage. However, there is no official method to test this, and most manufacturers design their own methods, chiefly requiring some type of subjective shaking. The stability of the suspensions is partly dependent on the particle size in suspension. This can be measured using techniques such as laser diffraction and Malvern Mastersize (19). As the stabilized suspension is mostly in a flocculated form, owing to the electrolytes added to it, it may be necessary to apply sonification in the study of particle sizes.