Nanosuspensions

A nanosuspension is a submicron colloidal dispersion of pure drug particles, which possess a large surface area for enhanced dissolution. Dissolution rate, depending on surface area and other factors, can be represented by the Noyes–Whitney equation:

$$\frac{dC}{dt} = \left(\frac{DS}{h}\right)(C_s - C)$$

where dC/dt is the dissolution rate, D is the diffusion coefficient, S is the surface area, h is the diffusion layer thickness, C_s is the saturated solubility, and C is the concentration of the drug in bulk solution.

Water-insoluble drugs can be formulated as nanoparticles with high surface area and enhanced dissolution rates accompanied with reduced drug particles. Administering a compound as small particles of defined size may be superior to, for example, a cosolvent formulation. In the latter case, precipitation, particle size of the precipitate, and site of precipitation *in vivo* are difficult to control or predict from *in vitro* experiments (Pannuti et al., 1987). Assuming drug particles are in a near spherical shape, a reduction in particle size from 10 μm to 200 nm increases drug surface area by 50-fold, which may have a profound effect on drug absorption. For a drug with dissolution rate-limited bioavailability, particle size reduction can significantly improve the PK performance of the drug (Liversidge and Cundy, 1995).

Nanoparticles are typically produced by wet milling, homogenization, or precipitation techniques (Liversidge and Cundy, 1995; Merisko-Liversidge et al., 2003; Douroumis and Fahr, 2007). Nanosuspensions are thermodynamically metastable, being prone to particle regrowth and hence surface stabilizers are used to maintain particle size. The choice and concentration of stabilizers are selected to promote the particle size reduction process and generate physically stable formulations. To be effective, the stabilizer must be capable of wetting the surface of drug substance and providing a steric or ionic barrier to prevent the nanoparticle from aggregation. Many commonly used pharmaceutical excipients such as the celluloses, pluronics, polysorbates, and povidones are acceptable stabilizers for generating physically stable nanoparticle dispersions (Liversidge and Cundy, 1995). Celluloses increase aqueous viscosity and retard sedimentation of suspended drug, thereby improving dose uniformity. Common formulation includes vehicles containing dispersion agents such as hydroxylpropyl cellulose in the range of 1%–3% and surfactants such as Docusate Sodium (DOSS) in the range of 0.1%–1%.

Nanosuspensions have found wide use in recent years for oral, injectable, inhalation, and intrademeral applications (Merisko-Liversidge et al., 2003). The nanosuspension technology is extremely useful for conducting various screening studies with poorly water-soluble drugs at the preclinical stage. As the formulation does not contain high levels of excipients (cosolvents, surfactants), results of such studies can be more precisely correlated with the candidate molecule. The method has many formulation and therapeutic advantages, such as a relatively simple method of preparation, lower requirement for formulation excipients, reduction in the toxicity of the candidate drug, significant increase in the bioavailability leading to decrease in the optimal dose, decreased fed-fasted variability, and so forth (Rabinow, 2004; Wu et al., 2004; Dubey, 2006). One of the main applications of nanosuspension has been the formulation of pharmaceutical compositions that can be administered intravenously. For intravenous administration of a suspension, the particles in the suspension need to be less than 5 μm, which is the diameter of the smallest blood capillaries in the body. Intravenous administration of the nanosuspension may result in advantages such as no higher concentration of toxic cosolvents and improved therapeutic effect of the drug available as a conventional oral formulation. Nevertheless, several products are now available based on nanosuspension principles.