Table 9-6 Relative Properties of Deflocculated and Flocculated Particles in Suspension

State	Particle characteristics	Sedimentation rate	Appearance	Cake	Resuspension
Deflocculated	Exist as separate entities	Slow	Initially suspended, but settles to a small volume	Yes	Difficult to redisperse
Flocculated	Exist as weak aggregates (floccules)	Fast	Settling results in the presence of an obvious, clear vehicle region. Final volume may be large or small	No	Easy to redisperse

agitation. Ultralente insulin is an example of a suspension that displays a very small sedimentation volume, but the particles are easily resuspended to homogeneity with gentle shaking of the vial. Because Ultralente insulin crystal growth conditions are defined and the suspension has appropriate stability, there is little value in making adjustments to improve its physical appearance upon settling. Thus, suspension formulation design may require compromises between aesthetic aspects and other desirable physical attributes of the preparation.

Sedimentation volume and zeta potential measurements are useful for optimizing the physical properties of suspensions by providing information on the degree of flocculation. Sedimentation volume is determined by measuring the equilibrium volume of settled particles relative to the total suspension volume after resuspension. The quantity is expressed as a ratio:

$$F = V_u / V_o \qquad \text{(Equation 1)}$$

where V_u is the equilibrium volume of sediment and V_o the total suspension volume.

Zeta potentials are determined to estimate surface charges. The relationship between sedimentation volume and zeta potential is illustrated in Figure 9-4. The addition of a flocculating agent causes a progressive reduction in zeta potential and changes in sedimentation volume. There exists a region where the sedimentation volume is maximized (flocculated) and no caking is observed. Note that if too much flocculating agent is added overflocculation and caking can occur. Exposing suspensions to extremes in temperature or mechanical stress can also produce this effect. This example indicates that the zeta potential must be controlled in order to produce a suspension with desirable physical properties.

Another method besides controlled flocculation for achieving optimal physical stability of suspensions is termed the structured vehicle approach. In this case, viscosity-imparting suspending agents, such as sodium alginate, glycerin, or sodium CMC, are added to the vehicle to reduce sedimentation and maintain the particles in suspended state. The vehicle is described as having pseudoplastic or plastic flow, is preferably thixotropic, entraps suspended drug particles to prevent or slow settling properties, and its shear thinning properties facilitates particle resuspension. In most situations, structured vehicles are not appropriate for parenteral preparations because vehicle viscosity is too high, adversely affecting syringeability.

Crystal Growth, Caking, and Syringeability

Three primary problems occur with dispersed systems—crystal growth, caking, and syringeability. Crystal growth occurs when drug particles stick together to form larger particles such that they cannot be redispersed easily and the uniformity of drug particles per unit volume is unequal. Caking occurs when the drug particles settle to the bottom of the container and pack so tightly that no amount of agitation (shear force) can cause the particles to resuspend. Syringeability refers to the ease or difficulty in withdrawing the suspension from the container through a narrow needle into the syringe.

To overcome crystal growth, selection of appropriate suspending agents and viscosity-inducing agents to coat drug particles and reduce the rate of particle settling according to

$$K_{cg} = Ae^{-\alpha\eta+\beta} \qquad \text{(Equation 2)}$$