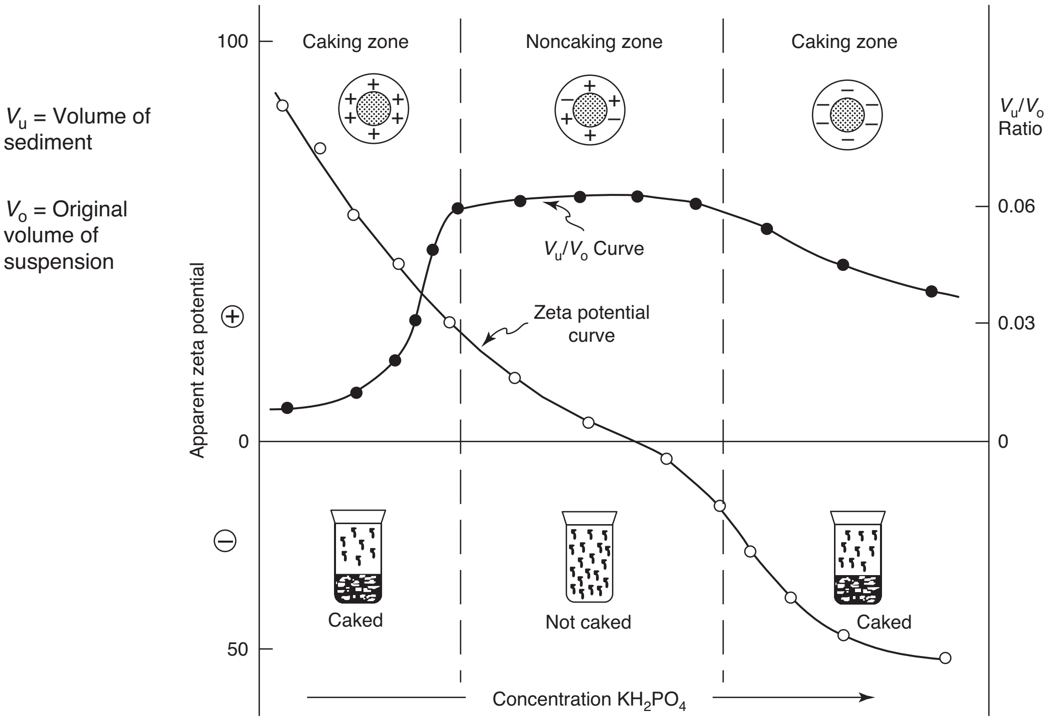

Figure 9-4 Relationship between zeta potential and sedimentation volume. The diagram depicts the effect of adding an anionic flocculating agent to a positively charged system. Maximum flocculation, as determined by sedimentation volume measurements, occurs within a narrow range of zeta potential values. The region designated as "noncaking zone" defines formulation conditions where caking of the suspension is less likely to occur. *Source*: From Ref. 14.

where crystal growth (K_{cg}) is inversely proportion to the log of viscosity (η). Particle size distribution, dissolution and recrystallization, pH and temperature changes, and polymorphism and solvate formation are factors that can affect crystal growth. The close contact of particles in settled deflocculated suspensions will favor crystal growth by a process referred to as Ostwald ripening (15).

Retarding crystal growth by the addition of viscosity-imparting agents usually is not appropriate for parenteral suspensions. Increasing viscosity of the vehicle (continuous phase) will help to a point, beyond which syringeability issues may be prominent. The best approaches for minimizing crystal growth in suspensions are to control the particle size distribution, select the correct polymorph (if applicable), or use the controlled flocculation approach. Appropriate testing should also be conducted to determine the impact of pH and temperature changes on physical stability. Milling methods that produce a narrow particle size distribution range also help to minimize packing, caking, and crystal growth of particles. Using amorphous additives like polymers that do not crystallize will help.

Caking of suspensions can be minimized by following the principles of Stokes Law

$$Y = \frac{2r^2(\Delta\rho)g}{9\eta} \qquad \text{(Equation 3)}$$

where Y is the "terminal velocity" or the rate of settling (m/sec) leading to caking, r^2 is the radius squared (m^2), $\Delta\rho$ is the difference in density between the dispersed phase (drug particle) and the continuous phase (vehicle) (kg/m^3) g is gravitational acceleration (m/s^2), and η is the vehicle viscosity ($kg\ m^{-1}\ sec^{-1}$). Therefore, the rate of setting can be reduced if the particle size is reduced, the density differences between suspended particles and vehicle are minimal, and the vehicle viscosity is increased.