

zone, changing the nature of the system from a deflocculated to a flocculated one. Further outward movement will take the particles out of the secondary minimum zone and into an area of very little interaction, again changing the nature of the suspension, this time from a flocculated to an effectively deflocculated system. Decreasing the separation distance between particles will initially move them from the secondary minimum zone, showing flocculated behaviour, to the primary maximum zone, showing deflocculated behaviour. Further inward movement will result in the particles entering the primary minimum zone, leading to irreversible coagulation. It must be remembered that gravity works only in one direction (downwards) and that the base of the container is immobile, so ultimately the first settling particle or floccule will reach a point at which its travel stops and it rests on the inside bottom surface of the container. The second and subsequent sedimenting particles or floccules will then approach the first, fixed one, from above. The combination of gravitational force on the sedimenting particles or floccules and mechanical forces exerted by the mass of the sedimenting particles or floccules on those below will overcome V_R , moving the particles into the primary minimum zone and irreversible coagulation.

Controlling the movement of particles within the suspension formulation is extremely important to maintain the desired flocculation status. Examination of Equations 3.30 and 26.3 that control diffusion and sedimentation respectively, will allow assessment of which factors can be manipulated and the likely results of such manipulation.

1. a , the radius of the particle. Manipulation of particle size is relatively easily accomplished mechanically or via manipulation of crystallization techniques. Reducing particle size will increase diffusion and reduce sedimentation, with a larger effect on the sedimentation rate. Particle size reduction would generally be regarded as beneficial because of these effects. However, particle size is a key parameter governing particulate interactions as described by the DLVO theory and so manipulation of particle size will have a direct effect on V_T and flocculation behaviour. Particle size will also have an effect on the dissolution behaviour of the drug, which is discussed below.

2. ρ , the density of the particle. Particles are generally denser than the medium in which they are dispersed, and the greater the density difference,

the faster the sedimentation rate. Reducing the particle density by changing crystallization methods is possible, but this will result in an increased particle size (if the total number of particles remains constant) or an increased number of particles (if the particle size remains constant); both of these leading to a change in the DLVO characteristics and flocculation behaviour of the system. So, although manipulation of the density of the particles seems an easy way of reducing the sedimentation rate, it has potential serious disadvantages. Diffusion is unaffected by particulate density.

3. ρ_0 , the density of the medium. Reducing the density difference between the particles and the medium will lead to a reduction in sedimentation rate, which is beneficial for pharmaceutical suspensions. This is most easily achieved by increasing the density of the medium. Although most pharmaceutical suspensions are based on water, addition of materials such as dextrose or some polymers will raise the density of the product sufficiently to reduce the observed sedimentation. It is best if these materials are non-ionic, as ionic materials will lead to a change in the flocculation behaviour of the particles, via movement of the counter-ion into the diffuse layers surrounding the particles.

4. η , the viscosity of the medium. Raising the viscosity of the medium will reduce diffusion of the particles, with a value of 5 mPa s effectively decreasing the diffusion to zero. An increased viscosity will also reduce the particulate sedimentation rate. Overall, an increased viscosity is beneficial for pharmaceutical suspensions. The viscosity of water is very low (1 mPa s at 20 °C), but it can be easily modified via additives such as polymers, for example hydroxypropyl methylcellulose or sodium carboxymethylcellulose. In the latter case, however, effects on the electrical double layer around the particles and hence flocculation behaviour are likely to be seen due to the mobile Na^+ ion.

5. T , temperature (in Kelvin). Increasing the temperature will lead to an increase in the diffusion constant and hence greater particle mobility. Although not expressed explicitly in Equation 26.3, the viscosity of a given substance will change with temperature, affecting both diffusion and sedimentation. In reality, however, the range of temperatures to which a suspension is exposed (or should be exposed) is limited but uncontrolled outside the place of manufacture, and temperature should not be used as a tool with which to control particulate