

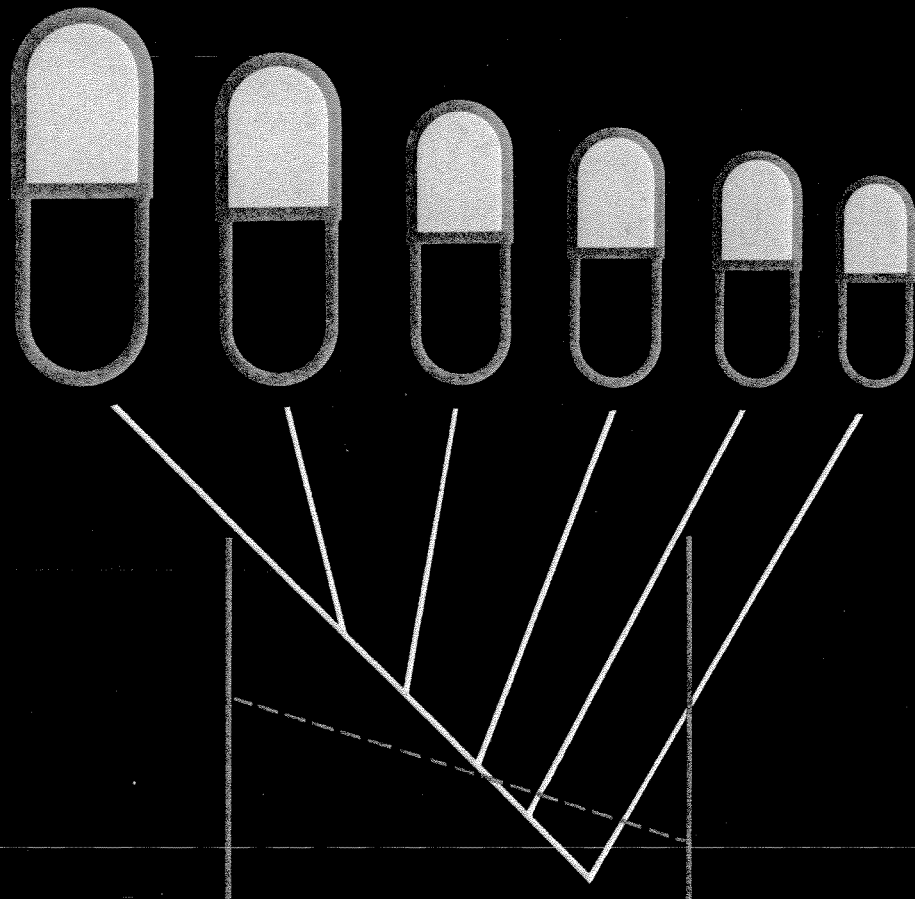
MODERN PHARMACEUTICS

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IV. SUSPENSIONS

A. Advantages and Disadvantages of Suspension as a Dosage Form

Even those of use who have invested considerable time and labor in the formulation of suspensions must admit that the suspension has a number of disadvantages as a dosage form. First, uniformity and accuracy of dose, even when the preparation is nurse administered, is unlikely to compare favorably with that obtainable by the use of tablets or capsules. Sedimentation and compaction of sediment cause problems which are by no means always easy to solve. Further, the product is liquid and relatively bulky; these properties are disadvantageous to both pharmacist and patient. Formulation of an effective and pharmaceutically elegant suspension is usually much harder to achieve than of a tablet or capsule of the same drug. However, suspensions do have some advantages which can, under certain circumstances, outweigh their disadvantages.

Many of the more recently developed drugs are basically hydrophobic in nature and thus their aqueous solubilities are low. Thus solutions of these drugs, containing an appropriate dosage, would be of an unacceptably large volume. Suspensions allow the development of a liquid dosage form containing an appropriate quantity of drug in a reasonably small volume. Further, resistance to hydrolysis and oxidation is generally good compared with that observed in aqueous solution. Suspensions can also be used to mask the taste of drugs. Also, there is a significant proportion of the population, especially very young children, who have difficulty in swallowing tablets or capsules. In recent years increasing attention has been given to the use of suspensions in intramuscular injection for depot therapy. For example, a number of research teams are presently developing intramuscular suspensions of contraceptive steroids that may give contraceptive protection for periods in excess of a year.

B. Physical Stability of Suspensions

Pharmaceutical suspensions are basically unstable systems. Aggregation of suspended particles and sedimentation (and possibly impaction of sediment) present real problems to the pharmaceutical formulator. As has already been indicated, much of the theory relevant to the formulation of acceptable pharmaceutical suspensions is derived from the findings of colloid scientists who have studied model systems. There are, however, several important differences between model colloidal systems and pharmaceutical suspensions, some of the more important of which are shown in Table 6.

Repulsive and Attractive Forces Between Particles

Much of the present-day theory regarding the charge on suspended particles results from the work of four scientists: Derjaguin and Landau from the Soviet Union, and Verwey and Overbeek from the Netherlands. The theory is thus often referred to as the DLVO theory. This theory allows us to develop insight into the factors responsible for controlling the rate at which particles in a suspension will come together, or aggregate, to form duplets (two particles), triplets (three particles), and so on. The process of aggregation will accelerate sedimentation and affect redispersibility and thus is important to the pharmaceutical scientist formulating a suspension. The total energy of interaction, V_T , between two particles is defined as

Table 6. Differences Between Colloidal and Pharmaceutical Suspensions

Model colloidal suspensions	Pharmaceutical suspensions
Homodisperse (i.e., suspended particles almost all the same size)	Heterodisperse (i.e., suspended particles of a considerable range of sizes)
Particles less than about 1 μm in diameter	Particles often very much larger than 1 μm
Continuous phase simple in nature; basically aqueous	Continuous, often complex: containing many substances as well as water
Shapes of particles usually close to spherical	Shapes often quite nonspherical (e.g., needle crystals)
Solids content usually low (e.g., 2%)	Solids content sometimes very high (e.g., 50%)

$$V_T = V_R + V_A \quad (5)$$

where V_R and V_A represent the repulsive and attractive forces, respectively. (It is possible to estimate V_R and V_A ; see Matthews and Rhodes [23]). Figure 2 exemplifies some energy-of-interaction curves. Curve A applies when $V_R > V_A$, that is, the term V_T is always positive because of the high potential at the double layer. In such cases a suspension would exhibit very good resistance to aggregation (i.e., flocculation or coagulation) provided that the particles are not sufficiently large to sediment under gravity.

Curve B shows a high potential energy barrier, V_M , which must be surmounted if the particles are to approach one another sufficiently closely to enter the deep primary energy minimum at P. If the height of the energy barrier V_M greatly exceeds the mean thermal energy of the particles, they will not be able to enter P. The value V_M required to just prevent this is probably equivalent to a zeta potential of about 50 mV. Thus, in formulating a pharmaceutical suspension it is often useful to aim at a system with a zeta potential of more than 50 mV. Aggregates that do form at P are likely to be very tightly bound together since H, the interparticulate distance, is small and the energy well at P is often quite deep. Thus in a pharmaceutical preparation very vigorous shaking would be required to redisperse the product. It should also be noted that there is a secondary energy minimum at S. If this trough is sufficiently deep, loose aggregates can form at this point; these will usually be easy to redisperse.

Curve C shows the situation that exists when attractive forces completely overwhelm repulsive forces (i.e., $V_A > V_R$). Under other such conditions very rapid aggregation will occur.

The curve V_S shows the stabilizing effect of surfactants adsorbed on the surface of suspended particles; it shows a quite sharp cutoff point at $2d$, where d is the thickness of the adsorbed surfactant layer. The strongly hydrated nature of surfactant head groups impedes particle-particle

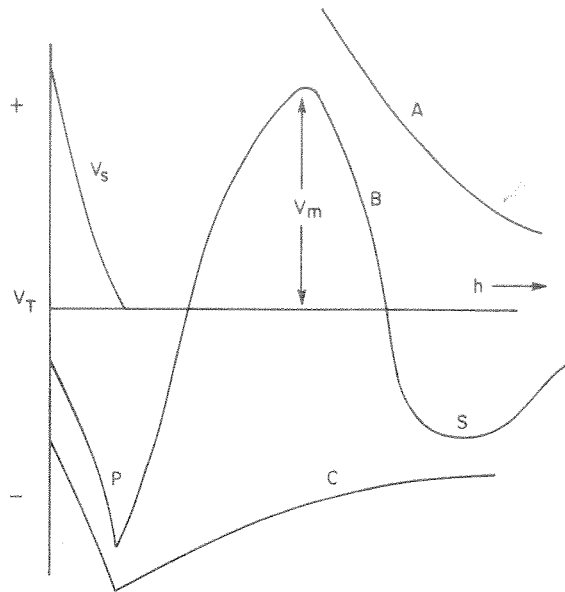


Figure 2 Total energy of interaction curve between suspended particles (h is the interparticulate distance).

contact, which would result in aggregation. Thus, even nonionic surfactants can be used to stabilize suspensions. It should be noted, however, that an excessive quantity of surfactant can, in some systems, have a significantly adverse affect on stability.

Aggregation Kinetics

The aggregation of particles in a suspension can be termed flocculation or coagulation. The term coagulation should be used when the forces involved are primarily physical due to reduction in the repulsive forces at the double layer. The term flocculation is applied to those cases in which "bridging" occurs between particles. However, since in many pharmaceutical systems the exact nature of the forces is somewhat obscure, we shall restrict ourselves here to use of the term aggregation. Using simple diffusion theory [24], Von Smoluchowski derived equations for both rapid aggregation (when all particle-particle collisions result in aggregation) and slow aggregation (in which only a fraction, α , of all particle-particle collisions result in the formation of aggregates). Pharmaceutical scientists are concerned primarily with slow aggregation, since the aggregation in suspensions of drugs is mainly slow. The $t_{1/2}$, time for the initial number of particles (singlets) in a suspension to decrease by 50%, because of aggregation is given by

$$t_{1/2} = \frac{1}{4D_1RN_0\alpha} \quad (6)$$

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