Orthokinetic Coagulation in Pharmaceutical Suspensions

Keyphrases ☐ Suspensions, pharmaceutical—orthokinetic coagulation due to sedimentation and laminar shear ☐ Coagulation (orthokinetic), suspensions—based on sedimentation and laminar shear

Sir:

The classical theory of perikinetic coagulation of lyophobic colloids was developed by Smoluchowski (1) for spherical uniformly sized particles undergoing diffusion as a result of Brownian motion. Attempts to apply the Smoluchowski theory to pharmaceutical suspensions are of limited success for the following reasons.

Particle Size—In pharmaceutical suspensions, most of the particles are of dimensions greater than the upper limit for lyophobic colloids, which is usually put at 0.5-μm. diameter (2). The basic equations derived by Smoluchowski for the coagulation rate of particles in these systems (3) have no term for particle size, but it was previously reported (4) that a 1.1-μm. diameter polystyrene latex has a slower maximum coagulation rate than one of 0.7-μm., whose rate was also slower than the Smoluchowski theory. Such deviations from theory were explained by Higuchi *et al.* (5) in terms of hydrodynamic effects. From the Smoluchowski theory, it may be calculated that the 2.5% (w/v) suspensions of the drug griseofulvin, described earlier (6), would have a coagulation time (*i.e.*, time to reduce the original particle concentration by one-half) of 6 sec. if the particles were 1.0 μm. in diameter and of 100 min. if they were 10 μm. in diameter. In the latter case the particles would be subject to rapid sedimentation and to only relatively little Brownian motion. It has been shown (7) that for griseofulvin suspensions, Brownian motion is theoretically a greater source of displacement than sedimentation up to a diameter of 1.7 μm. Above this figure the reverse applies.

Polydispersity—The Smoluchowski theory was extended by Müller (8) to allow for polydispersity. This theory was shown by Matthews and Rhodes (9) to apply qualitatively to particles in the size range of 0.5–2.0 μm.

Dimensional Anisotropy—Müller (10) also extended the Smoluchowski theory to allow for nonspherical particles. He showed that these should coagulate more rapidly than spherical ones and this was confirmed by Wiegener and Marshall (11).

Nature of the Interface—Many powdered drugs that are formulated as aqueous suspensions are truly hydrophobic and must be wetted prior to dispersion. The use of amphipathic adjuvants for this purpose is likely to effect steric stabilization of the particles (12, 13).

The question of whether or not drug particles may be flocculated or coagulated in an analogous way to lyophobic colloids to prevent impaction on storage was discussed extensively in the literature (6, 13–18). Because of the previously mentioned differences between lyophobic colloids and drug suspensions, it can be misleading to apply criteria derived from colloid chemistry to differentiate between aggregation mechanisms in coarse systems. For example, coagulation in a lyophobic colloid produces a compact sediment whereas flocculation yields a porous compressible structure. However, when a suspension of highly dispersed drug particles is allowed to sediment, a compact structure usually is produced. An evaluation of such a suspension on the basis of criteria taken from colloid chemistry would suggest that it had coagulated. A state of a high degree of dispersion or peptization is, however, the exact opposite of coagulation in true colloids. When the forces causing particle dispersion in a suspension are removed, coagulation occurs. Since Brownian motion cannot be considered as the main cause of coagulation in the case of pharmaceutical suspensions, it has been tentatively suggested (13) that differential sedimentation rates could cause the necessary particle collisions. Theories of orthokinetic coagulation, where the causative agent is systematic movements within the system (*e.g.*, sedimentation) were formulated by von Smoluchowski (1), Tuorila (19), and Müller (10). Hiestand (20), in his comprehensive review of coarse suspensions, differentiated between the effects of sedimentation on peptized and aggregated systems and described cases in the literature where agitation was shown to accelerate flocculation. As far as is known, however, no attempt has been made to interpret aggregation processes in pharmaceutical systems using these early theories (1, 10, 19). This is the purpose of the present communication. Two types of orthokinetic coagulation that could occur in pharmaceutical suspensions will be considered.

Coagulation Due to Sedimentation—Whereas the theory for perikinetic coagulation was formulated for a monodispersed suspension, coagulation due to sedimentation can only occur if the system is polydispersed. Müller (10) considered a large spherical particle of radius R sedimenting under gravity with a speed V_R in a rapidly coagulating colloid containing, at time t_0, N_0 spherical particles of radius r. Brownian motion of the large particle and sedimentation of the small ones are initially ignored. He derived the following equation to express the number of small particles, dN, that coagulate with the large one in time dt:

$$\frac{dN}{dt} = 4\pi N_0 D x \frac{\sinh C}{C} \qquad \text{(Eq. 1)}$$

where D is the diffusion constant of the small particles and x is the collision radius of the large and small particles $= r + R$. The value of C is defined by the equation:

$$C = \frac{V_R}{D}\left[x - R\left(\frac{3}{2}\ln\frac{x}{R} + \frac{R^2}{4x^2} + \frac{3}{4}\right)\right] \qquad \text{(Eq. 2)}$$

Since the rate at which the small particles would be expected to coagulate with large ones is given according to the Smoluchowski theory by the equation:

$$\frac{dN}{dt} = 4\pi N_0 D x \qquad \text{(Eq. 3)}$$

the probability of coagulation when one of the particles

Table I—Dependence of the Value of the Müller Constant C on the Radii of the Coagulating Particles in a Suspension of Fine-Particle Griseofulvin

r, μm.	R, μm.	(α)	R^4	$f(\alpha)$[a]	C
0.5	10	0.05	10^{-12}	2.4×10^{-6}	0.107
1.0	10	0.1	10^{-12}	3.6×10^{-6}	1.601
5.0	10	0.5	10^{-12}	7.7×10^{-3}	342.4
8.0	10	0.8	10^{-12}	1.46×10^{-2}	649.3
9.0	10	0.9	10^{-12}	1.10×10^{-2}	493.6
0.5	5	0.1	6.25×10^{-14}	3.6×10^{-5}	0.100
1.0	5	0.2	6.25×10^{-14}	4.5×10^{-4}	1.25
2.0	5	0.4	6.25×10^{-14}	4.25×10^{-3}	11.81
4.0	5	0.8	6.25×10^{-14}	1.46×10^{-2}	40.57
4.5	5	0.9	6.25×10^{-14}	1.10×10^{-2}	30.57
0.5	2.5	0.2	3.90×10^{-15}	4.5×10^{-4}	0.078
1.0	2.5	0.4	3.90×10^{-15}	4.25×10^{-3}	0.737
1.5	2.5	0.6	3.90×10^{-15}	1.13×10^{-2}	1.959
2.0	2.5	0.8	3.90×10^{-15}	1.46×10^{-2}	2.53
2.25	2.5	0.9	3.90×10^{-15}	1.10×10^{-2}	1.910

[a] Data taken from Müller (10).

is sedimenting with a speed of V_R is increased by the factor sinh C/C.

When the ratio of the radii r/R is not very small, the Brownian motion of the large particle and sedimentation of the small ones have to be considered by the modified equation for the diffusion constant:

$$D = \frac{kT}{6\pi\eta}\left(\frac{1}{R} + \frac{1}{r}\right) \qquad \text{(Eq. 4)}$$

V_R is replaced by the relative sedimentation velocity, v, in Eq. 2 and the modified Stokes' law:

$$v = (V_R - V_r) = \frac{2}{9}\frac{\rho g(R^2 - r^2)}{\eta} \qquad \text{(Eq. 5)}$$

where ρ is the difference in density between the dispersed and continuous phases. The other symbols have their usual meanings.

By combining Eqs. 2, 4, and 5, Müller (10) derived the following expression for the value of C:

$$C = \frac{4\pi\rho g R^4}{3kT} f(\alpha) \qquad \text{(Eq. 6)}$$

where:

$$f(\alpha) = \alpha(1 - \alpha)\left[\alpha + \frac{\alpha(2 + \alpha)}{4(1 + \alpha)^2} - \frac{3}{2}\ln(1 + \alpha)\right] \qquad \text{(Eq. 7)}$$

and:

$$\alpha = \frac{r}{R} \qquad \text{(Eq. 8)}$$

Müller showed that for the sedimentation effect to be significant, the sedimenting particle should be larger than:

$$R \geq \sqrt[4]{\frac{40kT}{\pi\rho g}} \qquad \text{(Eq. 9)}$$

and the particles that are caught by the falling one should be larger than:

$$r \geq \sqrt[4]{\frac{1{\cdot}2\,kT}{\pi\rho g}} \qquad \text{(Eq. 10)}$$

It is now possible to consider the application of the Müller theory to the fine-particle griseofulvin suspensions described earlier (21). Using a value for ρ of 0.445 g./ml., the critical values for r and R are 0.77 and 1.85 μm., respectively. Measurement of the particle size of the drug by means of the Coulter counter (22) showed that most of the particles were between 0.5- and 10.0-μm. equivalent spherical radius. Therefore, values of C were calculated using values of R of 2.5, 5, and 10 μm. and of r within the range of 0.5–9.0 μm. The results are shown in Table I. The dependence of the ratio (sinh C/C) upon C is shown in Table II. When C = 2.1, the speed of coagulation is doubled; when $C > 5$, the sedimentation effect is so great that coagulation due to Brownian diffusion can be ignored. An inspection of Table I shows that for large particle radii, R of 10 and 5 μm., very pronounced effects due to sedimentation can be expected. Even for particles of R = 2.5 μm., an approximate twofold increase in coagulation rate can be expected for r values of about 1.5 μm. and above.

Table II—Relationship between the Müller Constant C and sinh C/C[a]

C	$\frac{\sinh C}{C}$	C	$\frac{\sinh C}{C}$
0	1	2	1.81
0.2	1.006	3	3.84
0.4	1.027	5	14.83
0.6	1.066	7	78.4
0.8	1.110	9	450
1	1.175	10	1100

[a] Data taken from Müller (10).

Similar calculations can be performed for other drugs and for different vehicles; for example, the suspension of fine-particle griseofulvin in 70% glycerol described earlier by Matthews and Rhodes (7) has a phase density difference of 0.272 g./ml., very similar to that of a suspension of hydrocortisone in water. For such systems the critical radii increase to r = 0.88 μm. and R = 2.11 μm. and a similar sedimentation effect would only be experienced with larger particles.

The use of a slow speed centrifuge was advocated by Jones (23) as a means of accelerating physical changes in suspensions. The Müller theory provides a possible method of quantizing the effect of centrifuging on particle coagulation since the centrifugal force can be substituted for g in Eqs. 6, 9, and 10. However, it is important to bear in mind that centrifuging may also cause the breakup of the loose coagulum at the base of the container, causing an impaction which may not occur under conditions of normal gravity.

Coagulation Due to Laminar Shear—The von Smoluchowski (1)–Tuorila (19) theory of laminar shear coagulation was conveniently summarized by Overbeek (24) and was used to interpret the flocculation of agitated suspensions of ferric oxide by Reich and Vold (25). The equation derived was:

$$\frac{J}{I} = \frac{\eta R^3(du/dz)}{2kT} \qquad \text{(Eq. 11)}$$

where J is the probability of collision due to motion in a laminar flow field of shear gradient du/dz, I is the probability of collision due to Brownian motion, η is

the viscosity of the medium, and R is the particle radius. Since the effect of laminar shear is independent of the particle density, the conclusions of Reich and Vold are also applicable to pharmaceutical suspensions. They calculated that for a shear gradient of 100 sec.$^{-1}$, J/I is 10^{-2} for 0.1-μm. diameter particles, 10 for 1.0-μm. diameter, and 10^{4} for 10-μm. diameter. This shows again that, at around a diameter of 1 μm., orthokinetic effects assume a greater importance in comparison with perikinetic.

Discussion—To produce a pharmaceutical suspension that will sediment to give an open-structured redispersible coagulum, two processes are necessary: (*a*) particle collisions in the suspension, and (*b*) controlled particle adhesion on contact.

This communication has indicated that, in the absence of Brownian motion, sedimentation and shear effects can cause the former and the magnitude of the latter can be estimated by calculating energy of interaction curves (13).

Coagulation could be produced in a pharmaceutical suspension by the application of controlled shear, but care would be necessary since shear can also reverse the process and cause a breakdown in the structure. The formulator must design the suspension so that shear forces induced by shaking the container achieve this purpose. The sedimentation effect is inherent in the nature of the system, provided that there is a density difference between the phases and the suspension is polydispersed. Most pharmaceutical suspensions containing finely milled powders may be expected to have a proportion of particles in the region where Brownian motion is operative, and this proportion can be significant if calculated by number. Brownian coagulation eventually produces aggregates which are large enough to take part in sedimentation coagulation.

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Compendial Dissolution Tests: Merits of Sequential over Standard Inspection Plans

Keyphrases ☐ Dissolution tests, compendial—statistical analysis, proposed sequential analysis inspection of dosage units ☐ Sequential analysis inspection—application in dissolution testing ☐ Inspection of tablet and capsule lots—sequential analysis plan for dissolution rate testing ☐ Sampling of tablet and capsule lots—sequential analysis inspection plan.

Sir:

Dissolution rate tests for tablets and capsules are destructive tests, so any acceptance inspection plan for this property that is included in a compendial monograph must be based on the results of the complete analysis of one or more randomly selected samples. All sampling inspection plans carry two inherent risks because the quality of the chosen sample or samples may not truly reflect the absolute quality of the lot. The first risk is that a lot whose absolute quality is acceptable will have to be rejected. This risk, designated α, has its greatest influence on the economics of production. The second risk is that a lot whose absolute quality is unacceptable will pass inspection. This risk, designated β, has its greatest effect on the therapeutic effectiveness of the lot and, hence, on the consumer.

This communication is concerned with computing the values of α and β that are inherent in the dissolution tests in USP XVIII (1) and NF XIII (2) and with proposing the adoption of an alternative test based on a sequential analysis plan (3). No attempt is made to address the equally important question concerning the meaningfulness, in terms of the bioavailability, of the presently defined criterion of good and bad dissolution behavior which is based on the time it takes for 60% of the drug to dissolve from its dosage form. Regardless of what criteria may be laid down to ensure bioavailability, it is essential that the inspection plan used is one that carries values of risks α and β that are consistent with production economy and therapeutic effectiveness.