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Controlled Flocculation of Coarse Suspensions by Colloidally Dispersed Solids I: Interaction of Bismuth Subnitrate with Bentonite

HANS SCHOTT

Abstract □ Deflocculated suspensions of coarse powders tend to cake as the individual particles settle out and form compact, cohesive sediments. Limited flocculation results in looser sediments because the settled-out flocs incorporate large amounts of the liquid suspending medium. Controlled flocculation of bismuth subnitrate suspensions was achieved by the addition of small amounts of bentonite. The interaction of the coarse, positively charged bismuth subnitrate particles in aqueous suspension with negatively charged, colloidally dispersed bentonite was investigated by measuring electrophoretic mobility, sedimentation volume, and viscosity. Gradual addition of bentonite dispersion to bismuth subnitrate suspensions first reduced the ζ-potential of the bismuth subnitrate particles from +28 mv to zero, then inverted it, and finally caused it to level off at −20 mv for bismuth subnitrate–bentonite weight ratios below 200. Owing to the much greater specific surface area of bentonite, the surface of the bismuth subnitrate lath-shaped crystals was completely covered by 0.5% of its weight in clay platelets. Adhesion was promoted by electrovalences between surface bismuthyl ions and cation-exchange sites of the clay and by secondary valences. The charge neutralization of bismuth subnitrate by bentonite was a heterocoagulation process: the addition of small amounts of the clay flocculated the bismuth subnitrate suspensions and eliminated caking. While the ζ-potential of the bismuth subnitrate particles leveled off when their surface was saturated with bentonite platelets, sedimentation volume and viscosity continued to increase when the clay concentration was increased further while maintaining the bismuth subnitrate concentration constant. The excess, nonadsorbed bentonite formed the characteristic house-of-cards structure, incorporating the bentonite-coated bismuth subnitrate particles as cornerstones.

Keyphrases □ Flocculation, controlled—coarse suspensions by colloidally dispersed solids, interaction of bismuth subnitrate with bentonite □ Suspensions, coarse—controlled flocculation by colloidally dispersed solids, interaction of bismuth subnitrate with bentonite □ Colloidal dispersions—controlled flocculation of coarse suspensions, interaction of bismuth subnitrate with bentonite □ Bismuth subnitrate—coarse suspension, controlled flocculation by colloidally dispersed bentonite □ Bentonite—colloidal dispersion, controlled flocculation of coarse suspension of bismuth subnitrate

The kinetic units in extensively deflocculated suspensions are primary particles or small aggregates. When approaching the bottom of the container during sedimentation, these particles can slip past one another, each seeking the lowest possible point, and settle down next to each other. They pack efficiently to produce compact, dense solid layers. The interparticle attraction in such compact sediments is high because the interparticle distances are small and the London–van der Waals forces, which decrease approximately with the seventh power of the distance, are consequently appreciable. Such conditions frequently lead to caking or claying, an undesirable phenomenon because it produces sediments that require extensive agitation for redispersion (1).

The kinetic units in flocculated suspensions are larger aggregates or flocs. They bridge easily when settling out and produce loose, voluminous sediments containing large amounts of trapped liquid suspending medium. Such sediments are easily redispersed into the original

flocs by shaking (1). These facts led to the development of the concept of controlled flocculation (2–7). By reducing the absolute value of the ζ-potential of the suspended particles, the van der Waals attractive forces between the particles overcome the coulombic repulsive forces. As a result, the primary particles adhere to one another in suspension and subsequently settle out as flocs, producing voluminous and readily redispersed sediments.

There are several techniques for causing suspensions to flocculate. According to the Schulze–Hardy rule and the underlying Derjaguin–Landau–Verwey–Overbeek theory, suspensions are flocculated most efficiently, i.e., at the lowest additive concentrations, by the addition of electrolytes where the counterion (the ion whose charge has the opposite sign of the charge of the particles) has a high valence (1, 7, 8). Additives that constitute exceptions to the Schulze–Hardy rule, promoting flocculation at much lower than predicted concentrations, include ionic surfactants and potential-determining ions of charge opposite in sign to that of the particles (1, 8). Flocculation by the addition of sensitizing levels of polyelectrolytes or other water-soluble polymers (1, 3, 7) is, according to the author's practical experience, difficult to control; small overdoses of polymeric flocculating agents may bring about peptization. These various techniques for producing controlled flocculation have been applied to suspensions of organic and inorganic pharmaceuticals (9–14).

The purpose of the present work was to investigate the use of colloidal dispersions of fine particle size to reduce the absolute value of the ζ-potential of coarse medicinal suspensions of opposite charge, thereby causing these suspensions to flocculate and to produce voluminous, easily redispersible sediments. It represents an extension of the concept of heterocoagulation (15, 16) to combinations of fine colloidal dispersions and coarse suspensions of opposite charges. Positively charged bismuth subnitrate was selected as the coarse particulate drug (4–6) while sodium bentonite represented the finely dispersed colloid. Much smaller amounts of the colloidal material than of the coarse solid are required for flocculation because the former has a far greater specific surface area.

The interaction of bentonite in aqueous dispersion with the coarse, negatively charged solid, microcrystalline cellulose, was reported previously (17).

EXPERIMENTAL

Materials—The two batches of bismuth subnitrate NF employed were designated Batch A[1] and Batch B[2]. Sodium bentonite[3] and the cation-exchange resin[4] were also commercial products. Water was double distilled. All other chemicals were ACS reagent grade.

Methods—Bentonite dispersions were prepared by slurrying 1 or 2% clay in a blender[5] with water. The dispersions were decanted from settled-out grit after 48 hr of standing. This step reduced their solids contents to 0.88 or 1.98% (w/w), as determined by drying aliquots to constant weight at 125°. These dispersions were quite alkaline (pH 9.2–9.6) and might, therefore, have promoted additional hydrolysis

of the bismuth subnitrate. Neutralization of the sodium bentonite by means of an acid would have added foreign electrolytes and might have leached some aluminum from the clay platelets. To avoid these undesirable effects, a small aliquot of the sodium bentonite dispersion was run through the cation-exchange resin in the hydrogen form. Enough of the acid bentonite dispersion (pH 2.0–2.2) was immediately added to the original, alkaline dispersion to lower the pH of the latter to between 5.2 and 5.5. The clay in these dispersions is referred to as sodium/hydrogen bentonite.

On standing, the pH of the sodium/hydrogen bentonite dispersions gradually increased by as much as 1 unit during the first 3–4 weeks and then became constant. The dispersions used in the present experiments were aged for over 4 weeks. Their pH values stabilized between 6.0 and 6.6.

The bismuth subnitrate suspension was prepared by the following successive steps: slurrying 120 g of powder with 600 ml of water, dispersing in a blender at top speed for 10 min, letting stand for 48 hr, filtering through a Büchner funnel (pH of filtrate = 1.44), washing three times with water, twice more resuspending in 500 ml of water by means of a blender, letting stand overnight, filtering (pH of filtrates = 1.6–1.9), washing once with water, and resuspending in the required volume of water by means of a blender. The final suspension was used for subsequent measurements within 8 hr. This procedure was designed to stabilize the composition of the surface layers of the bismuth subnitrate particles by causing surface hydrolysis to take place during the preparation of the suspension rather than during the measurements.

The solids contents of the three bismuth subnitrate suspensions employed, measured by withdrawing aliquots while the suspensions were being stirred and drying to constant weight at 105°, were 14.95, 17.72, and 23.46% (w/w).

To measure sedimentation volumes, 50-ml portions of the bismuth subnitrate suspension and measured volumes of water and sodium/hydrogen bentonite dispersion were pipetted, in that order, into 100-ml graduated cylinders equipped with standard taper stoppers. The water was added to bring the total volume to 70 ml for the first series and to 100 ml for the second. In the few instances where lower bismuth subnitrate–bentonite ratios were desired, some of the clear supernate of the 50-ml bismuth subnitrate suspension placed in the graduated cylinder was withdrawn and the 100-ml volumes were completed with clay dispersion. The contents were mixed by shaking, and sedimentation volumes were read after standing at rest for various lengths of time. The values were rounded to the nearest 0.5 ml. Measurements of pH were made with a combination glass and silver–silver chloride electrode and a digital pH meter[6]. When measuring the pH of the suspensions with two electrodes, equilibration times were far longer.

Microelectrophoresis measurements were made with a commercial instrument[7] using the molybdenum anode and an acrylic cell. The cell constant and equations for calculating specific conductance from current intensity, electrophoretic mobility from velocity of migration, and ζ-potential from electrophoretic mobility are given in Ref. 18.

Microelectrophoresis measurements are always made in very dilute suspensions to permit the determination of the velocity of migration of individual particles. The bentonite dispersions were diluted 1:100. The suspensions of bismuth subnitrate and the mixtures of clay dispersions and bismuth subnitrate suspensions were filtered and washed three times with water immediately prior to measuring electrophoretic mobilities to prevent hydrolysis of bismuth subnitrate from turning the suspensions acid. The washed solids were redispersed in water or in 0.001 or 0.01 M potassium chloride by manual shaking. Redispersing them briefly by means of a vortex genie shaker instead of manually did not change the mobility values significantly. In mixtures containing particles of bentonite and bismuth subnitrate, only the latter were used for mobility measurement. Their much larger size made them easily distinguishable from the much smaller clay particles. The pH values of the diluted mixtures were determined at the end of the electrophoresis measurements.

Viscosity measurements were made with a rotational instrument[8], using the largest (No. 1) spindle with the guard in place. The instrument was recalibrated with a 60% (w/w) sucrose solution. During

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Table I—Composition of Sodium/Hydrogen Bentonite–Bismuth Subnitrate Mixtures

Mixture	Bentonite, % (w/w)	Bismuth Subnitrate, % (w/w)	Weight Ratio $\left(\dfrac{Bismuth\ Subnitrate}{Bentonite}\right)$
1	0	13.18	∞
2	0.00114	13.18	11,560
3	0.00568	13.18	2,320
4	0.0114	13.18	1,160
5	0.0568	13.18	230
6	0.1136	13.17	115
7	0.2270	13.16	60
8	0	7.95	∞
9	0.0188	7.95	420
10	0.0375	7.95	210
11	0.187	7.94	40
12	0.374	7.93	20
13	0.561	7.92	14
14	0.747	7.91	10
15	0.932	7.90	8.5
16	1.320	7.88	6
17	1.651	7.86	5

Table II—Sedimentation Volumes of Sodium/Hydrogen Bentonite–Bismuth Subnitrate[a] Mixtures[b]

Mixture	Sedimentation Volume, ml, after 1 or 1.5 hr[c]	18 hr	pH of Filtrate after 18 hr
1	5[d]	5[d]	1.40
2	5[d]	5	1.40
3	6[d]	6	1.38
4	6.5[e]	6.5	1.37
5	8	7	1.36
6	12.5	9.5	1.35
7	14	12	1.37
8	7[d]	7[d]	—
9	7.5	7	1.51
10	9	7.5	1.49
11	22	21	1.72
12	35.5	32	1.73
13	52	43	1.75
14	60.5	51	1.75
15	82[d]	59	1.77
16	97.5	85	1.86
17	100[f]	88	1.93

[a] Bismuth subnitrate Batch A. [b] Total volume of Mixtures 1–7 was 70 ml and that of Mixtures 8–17 was 100 ml. [c] At 1.5 hr after mixing for Mixtures 1–7 and at 1.0 hr after mixing for Mixtures 8–17. [d] Supernate quite cloudy. [e] Supernate slightly cloudy. [f] No noticeable sedimentation and no separation of supernate of lower solids contents.

viscosity measurements of the suspensions, sedimentation of solid particles caused the shear stress (torque divisions) to drift downward. To prevent the settling out of solids from giving spuriously low viscosity values, the beaker containing the suspension was placed on a magnetic stirrer. Enough clearance was left between the bottom of the beaker and the viscometer guard to accommodate the stirring bar.

The suspension was stirred to distribute the sediment uniformly. Immediately after the stirring was stopped, the clutch of the viscometer was released and the reading was taken. While this technique did not permit the observation of thixotropic phenomena, the measurements could be made before appreciable sedimentation occurred and were, therefore, reproducible. Results are expressed as apparent viscosity in centipoises at 60 rpm. Temperature was constant at 24–25°.

The following technique was used to determine the effect of increasing concentrations of bentonite on the viscosity of bismuth subnitrate suspensions. The viscosity of a 750-ml portion of a suspension containing 26.7% (w/w) bismuth subnitrate was measured in a 800-ml beaker. The suspension was then permitted to undergo sedimentation. A 5-ml portion of clear supernate was removed, and 5 ml of a 2.19% dispersion of sodium/hydrogen bentonite was gradually added with stirring. After measuring the viscosity again and letting the suspension stand at rest, subsequent small portions of clear supernate were replaced by equal volumes of bentonite dispersion. Viscosity measurements were performed after each addition of clay. While the concentration of sodium/hydrogen bentonite was thus gradually increased, the concentration of bismuth subnitrate and the volume of the suspension remained essentially constant.

The last mixture had a high enough viscosity to make measurements at lower speeds. The revolutions per minute values were changed from 6 to 12 to 30 to 60 and back to 30 to 12 to 6. After each change of speed, the suspension had to be stirred to resuspend the sediment.

RESULTS

Two series of mixtures were made for the electrophoresis and sedimentation measurements. Each contained a constant level of bismuth subnitrate but a different amount of sodium/hydrogen bentonite. Sedimentation volumes and electrophoretic mobility were measured for each mixture. The compositions of the mixtures are listed in Table I.

Sedimentation Volumes—Sedimentation volumes for the 17 mixtures, measured after 1 or 1.5 and 18 hr, are listed in Table II. Sedimentation volumes after 18, 42, and 66 hr were the same. Therefore, the 18-hr values correspond to infinite time. The pH values are those of the filtrate, taken 18 hr after the bentonite dispersion and bismuth subnitrate suspension were mixed. The acidity is due to nitric acid produced by hydrolysis of the latter.

Electrophoretic Mobility—Electrophoretic mobilities for the mixtures of solids and their standard deviations are given in Table III. Each listed mobility value represents the average of 10 individual measurements, and the standard deviation is that of the average. Negative values indicate negative charges, which caused the particles to migrate to the positive pole. The factor to convert mobility values, in (micrometers per second)/(volts per centimeter), to ζ-potentials

Table III—Electrophoretic Mobility Values of Sodium/Hydrogen Bentonite, Bismuth Subnitrate[a], and Their Mixtures[b]

Mixture	Mobility $\pm$ s[c], $\left(\dfrac{\mu m/sec}{v/cm}\right)$	Specific Conductance, μmhos/cm	pH
In Water			
—[d]	-3.39 ± 0.07	40	7.7
—[e]	-3.04 ± 0.08	20	6.6
1	$+2.20 \pm 0.09$	5	5.1
2	$+2.08 \pm 0.14$	10	5.2
3	$+2.34 \pm 0.21$	10	5.2
4	$+0.53 \pm 0.05$	5	5.3
5	-0.81 ± 0.23	30	4.5
6	-1.67 ± 0.03	20	4.4
7	-1.61 ± 0.09	30	4.5
7f	$+1.57 \pm 0.14$	160	3.5
8	$+2.30 \pm 0.11$	100	4.0
9	-1.31 ± 0.12	30	5.9
12	-1.36 ± 0.09	30	6.3
13	-1.66 ± 0.08, -1.60 ± 0.09	30, 30	6.3, 6.0
16	-1.80 ± 0.13, -1.97 ± 0.18	10, 50	6.0, 6.0
In 0.001 M KCl			
9	-2.37 ± 0.32	200	4.7
10	-2.05 ± 0.13	210	4.6
11	-2.37 ± 0.11	200	4.6
12	-2.36 ± 0.11	200	4.5
13	-2.08 ± 0.13, -2.11 ± 0.09	230, 200	4.3, 4.4
14	-2.16 ± 0.15	200	4.6
15	-2.37 ± 0.13	200	4.5
16	-2.16 ± 0.07	200	5.9
In 0.01 M KCl			
13	-2.70 ± 0.09	1350	4.2
16	-2.75 ± 0.04	1350	—

[a] Bismuth subnitrate Batch A. [b] For mixtures of bentonite and bismuth subnitrate particles, mobility values refer to the latter only. [c] Average of 10 measurements $\pm$ SD of the average. [d] Pure sodium bentonite. [e] Sodium/hydrogen bentonite. [f] After triturating with mortar and pestle in water.
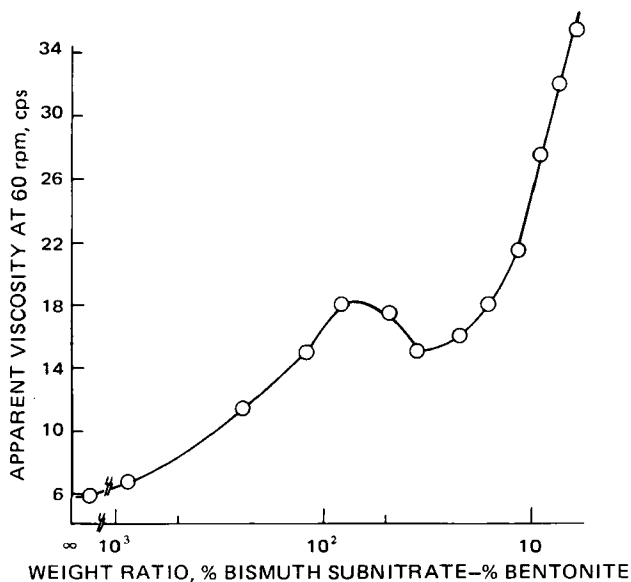
Figure 1—*Apparent viscosity as a function of composition, expressed as the weight ratio (percent bismuth subnitrate–percent bentonite), for a series of mixtures containing 26.73% (w/w) bismuth subnitrate.*

in millivolts is 12.9 according to the Smoluchowski equation at 25° (1, 18). At comparable pH and ionic strength, Batch B of bismuth subnitrate had twice the electrophoretic mobility of Batch A. For mixtures containing both bentonite and bismuth subnitrate, mobility values refer to particles of the latter only.

Viscosity—The apparent viscosity at 60 rpm as a function of the concentration ratio of bismuth subnitrate to sodium/hydrogen bentonite at a constant bismuth subnitrate concentration is shown in Fig. 1. The small maximum in viscosity followed by the shallow minimum in the range of concentration or weight ratios between 100 and 20 was replicated in a duplicate run. Figure 2 contains the consistency curve of the mixture with the lowest bismuth subnitrate–bentonite weight ratio and its apparent viscosity as a function of revolutions per minute. The two plots represent typical pseudoplastic behavior common to

suspensions and dispersions with relatively low volume fractions of the disperse solid phase (19).

Caking—Caking or claying of bismuth subnitrate suspensions was negligible for mixtures with bismuth subnitrate–bentonite weight ratios of 1200 or less. The sediments of these mixtures, formed after standing at rest for an hour or a week, were completely resuspended by inverting the container or by brief, gentle stirring. Thus, the addition of 0.1% bentonite, based on the weight of bismuth subnitrate, eliminated claying, which was severe in the absence of bentonite.

DISCUSSION

Bismuth subnitrate Batch A consisted largely of lath-shaped crystals (20). The average edge size, determined by microscopic examination, was approximately 3 μm. For cubes of density 4.92 g/cm^3, this dimension corresponds to a specific surface area in the neighborhood of 4300 cm^2/g.

Bentonite consists of elemental lamellas or individual lattice layers having a thickness of 9.4 Å (21). According to previous studies based on electron micrographs of diluted, dried, and shadow-cast dispersions, the primary particles of the type of bentonite employed here, when fully dispersed in water, are packets averaging 3–4 lamellas. This corresponds to an average thickness of 3.5 × 9.4 = 33 Å, not counting the water sheets intercalated between the lattice layers (22–24). The intracrystalline water is lost upon drying. At a density of 2.83 g/cm^3, platelets with a thickness of 33 Å have a specific surface area in the neighborhood of 2 × 10^6 cm^2/g, a value about 460 times greater than the specific surface area of Batch A. The average diameter of the primary clay platelets is 0.2 μm (22).

Thus, the primary bentonite particles in water are extremely thin and, hence, very flexible platelets. They were found to deposit on the surface of cotton fabric (22) and pulp fibers (24) from aqueous dispersions lying flat and molding themselves intimately to those surfaces, forming an uninterrupted film. This film averaged a mere 28–38 Å in thickness. Therefore, it replicated the topography of the cellulose substrates so completely that its presence could not be detected by electron micrographs of surface replicas. Cotton fabrics and paper covered by this very thin clay film had appearances identical to the original materials without the clay. On burning the cellulose substrates, the infusible clay film remained behind as a shrunken surface replica, preserving microscopic details of the topography of those substrates (22, 24). The adhesion of bentonite to cotton and paper occurs presumably by hydrogen bonds between the oxygen ions covering the clay platelets and the hydroxyl groups of cellulose.
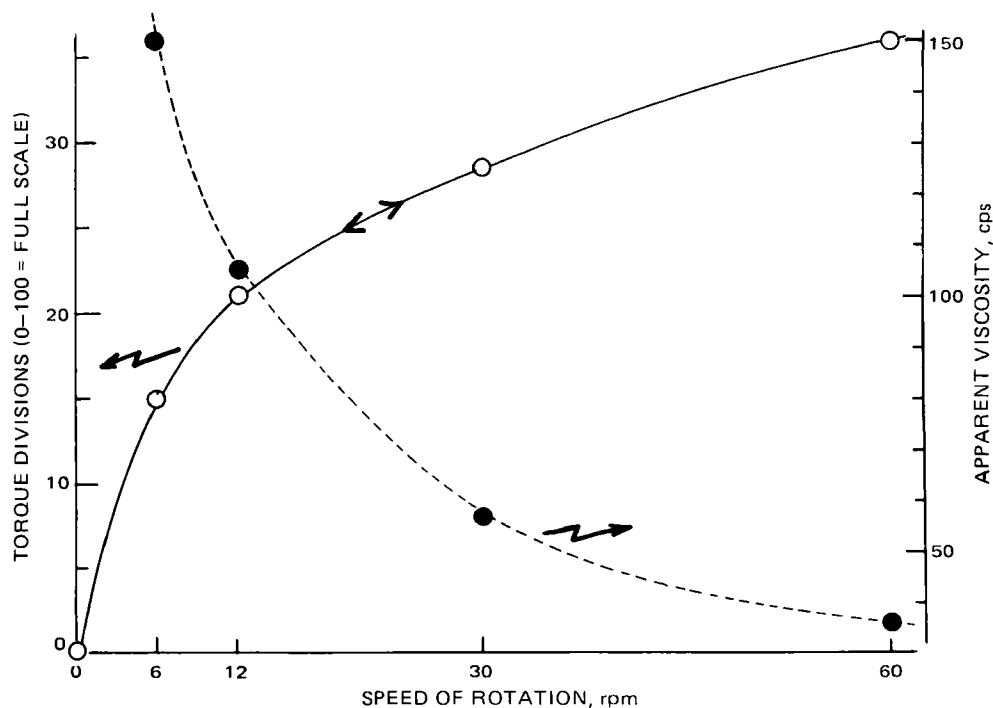

Figure 2—*Consistency curve and apparent viscosity as a function of rotational speed for a mixture of 26.73% bismuth subnitrate and 4.31% bentonite.*

The situation in the bentonite–bismuth subnitrate system appears to be analogous. In an aqueous dispersion, the sodium/hydrogen bentonite exists as very thin platelets. Partial substitution of sodium by hydrogen counterions did not alter the degree of dispersion of the bentonite in water (24). The clay platelets coat the large, lath-shaped bismuth subnitrate particles. The adhesion of the bentonite platelets to a bismuth subnitrate substrate is even stronger than to the cellulose substrates, because coulombic forces between the negatively charged clay and the positively charged bismuth subnitrate particles are superimposed on the van der Waals forces of attraction.

Bentonite particles owe their negative charge chiefly to cation-exchange sites, which are, in effect, silicic acid groups built into the clay lattice through isomorphous replacement of aluminum ions (Al^{+3}) by magnesium ions (Mg^{+2}) and silicon ions (Si^{+4}) by aluminum ions (Al^{+3}) (21). The counterions here are sodium and hydrogen cations. The electric charge of bismuth subnitrate particles in weakly alkaline, neutral, and acid media is positive because of an excess of bismuthyl cations over nitrate anions in the surface layer. The counterions are nitrate anions. When a bentonite dispersion is added to a bismuth subnitrate suspension, the extremely thin and smaller clay platelets lie flat against the surface of the coarse bismuth subnitrate crystals and adhere them. As the bismuth subnitrate surfaces become coated with bentonite platelets, their nitrate counterions are replaced by silicate ions embedded in the bentonite platelets. The sodium and hydrogen countercations of the latter pair off with the nitrate counteranions of the former, as illustrated in Fig. 3.

This arrangement is corroborated by the electrophoresis data of Table III. The addition of increasing amounts of bentonite dispersion to bismuth subnitrate suspensions gradually reduced the positive electrophoretic mobility or ζ-potential of the bismuth subnitrate particles to zero. This trend is shown by Mixtures 1–4 in Table III. Zero mobility corresponds to zero net charge, which indicates that the positive charges in the still bare portions of the surface of a bismuth subnitrate particle are equal in magnitude to the negative charges of the portions of that surface covered by sorbed bentonite platelets.

Further addition of bentonite beyond the amount that reduced the mobility of the bismuth subnitrate particles to zero inverted the sign of the mobility and conferred increasingly greater negative mobility values to these particles. This result is shown by Mixtures 5 and 6. The reason for the charge inversion is that the positively charged surfaces of the bismuth subnitrate crystals became more extensively covered with negatively charged bentonite platelets beyond the equivalence point. The net negative charge arises from the negative silicate ions in the outer face of sorbed clay platelets whose other face is attached to the surface of a bismuth subnitrate particle (Fig. 3).

However, the negative mobility values reached a limit. Despite continued increases in bentonite concentration, the electrophoretic mobility and the ζ-potential in water leveled off at −1.57 ± 0.25 (μm/sec)/(v/cm) and −20 ± 3 mv, respectively, for Mixtures 6, 7, 9, 12, 13, and 16. The level-off value for the negative mobility of bismuth subnitrate particles covered with bentonite platelets was one-half of the mobility of the bentonite platelets by themselves, which was −3.0 (μm/sec)/(v/cm). This finding is to be expected, because the cation-exchange sites in one of the two faces of a sorbed clay platelet are in contact with, and neutralized by, the bismuth subnitrate substrate. Only the negative charges in the outer face of a sorbed platelet, which are in contact with water and give rise to an electric double layer, contribute to the ζ-potential. In 0.001 M KCl, the plateau values for Mixtures 9–16 were −2.2 and −29 for mobility and ζ-potential, respectively.

The addition of bentonite to bismuth subnitrate to produce mixtures having bismuth subnitrate–bentonite weight ratios below 230 (in Mixtures 1–7, which contained 13% bismuth subnitrate) or below 420 (in Mixtures 9–16, which contained 8% bismuth subnitrate) caused no further increase in the negative values of electrophoretic mobility or ζ-potential. Evidently, the positively charged bismuth subnitrate particles became completely covered with negatively charged bentonite platelets at weight ratios below 230 (Mixture 5), producing saturation sorption. That ratio must be greater than the ratio of Mixture 6, namely, 115, because the bismuth subnitrate particles in that mixture already reached the plateau mobility.

It is of interest to compare the specific surface areas of bentonite and bismuth subnitrate with the weight ratio at which saturation sorption was reached. If the specific surface area of bentonite is 460 times greater than that of bismuth subnitrate, the bentonite platelets should completely cover the surface of the bismuth subnitrate particles at a bismuth subnitrate–bentonite weight ratio of 230. This
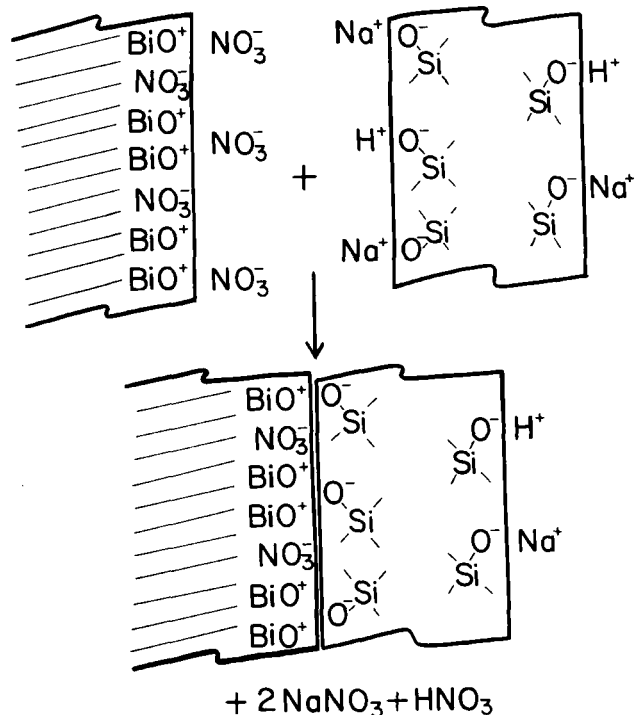

$+ 2NaNO_3 + HNO_3$

Figure 3—*Schematic representation in cross-section of the sorption of a segment of a bentonite platelet onto the surface of a bismuth subnitrate particle.*

value is one-half of the bentonite–bismuth subnitrate surface area ratio, because only one face of a bentonite platelet can contact a bismuth subnitrate surface and cover it. The effective surface area of bentonite for covering a solid substrate is, therefore, only one-half of the total value.

The weight ratio for complete coverage of bismuth subnitrate by a monolayer of nonoverlapping lamellas of bentonite 33 Å thick is 230. In practice, the sorbed clay platelets are likely to overlap. This overlapping reduces the effective specific surface area of bentonite dispersed in water and places the weight ratio for complete coverage or saturation sorption at below 230. The fact that this result is identical with the one obtained by electrophoresis is coincidental, because there is a gap between the weight ratios of Mixtures 5 and 6 and because the specific surface areas are only approximate values. The fact that the values obtained by electrophoresis and geometrical considerations are at least of the same order of magnitude corroborates the physical picture sketched in Fig. 3.

When Mixture 7 was triturated prior to electrophoresis measurements, fresh bismuth subnitrate surface was exposed, which was not previously in contact with, and therefore had not become coated by, bentonite. This fresh surface was positively charged and conferred positive values to the ζ-potential of the bismuth subnitrate particles.

A noteworthy feature of Table III is that the negative values of electrophoretic mobility and ζ-potential became more negative for a given mixture as the medium was changed from water to 0.001 and 0.01 M KCl. The usual effect of increasing ionic strength is to reduce the absolute values of electrophoretic mobility and ζ-potential. The present unusual behavior was reported for pure bentonite dispersed in aqueous solutions of the chlorides and sulfates of sodium and potassium (25).

Comparison of Table I with II and inspection of Fig. 4 show that the sedimentation volumes increased monotonically with decreasing bismuth subnitrate–bentonite weight ratios. For the mixtures containing 13% bismuth subnitrate (Mixtures 1–7), the rate of increase in sedimentation volume with a decreasing weight ratio was greatest in the vicinity of Mixture 5. Likewise, at approximately this same composition, the electrophoretic mobility of the bismuth subnitrate particles underwent the greatest variation, including a change in sign, and had the smallest absolute values. Small absolute values for mobility and ζ-potential cause the electrostatic repulsion between particles to be weak, promoting flocculation and large sedimentation volumes. The two curves in Fig. 4, representing electrophoretic mo-
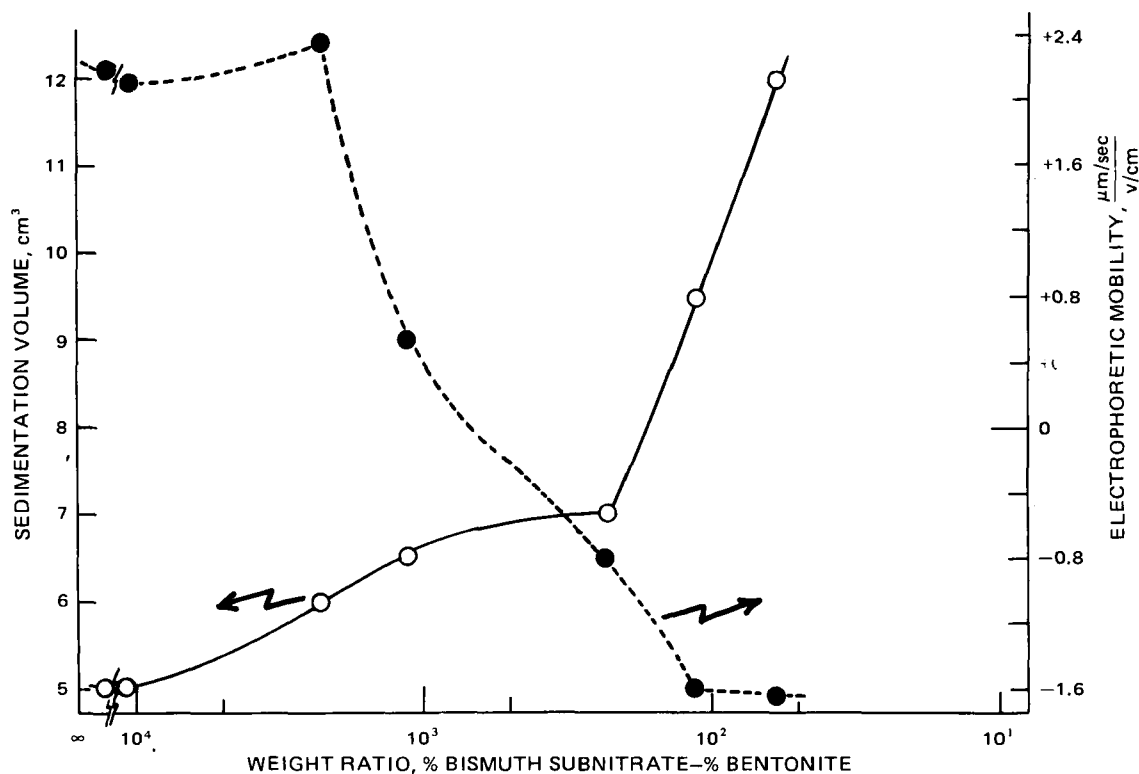
Figure 4—*Electrophoretic mobility and sedimentation volume at infinite time for Mixtures 1–7 as a function of the weight ratio (percent bismuth subnitrate–percent bentonite).*

bility and sedimentation volume as a function of the bismuth subnitrate–bentonite weight ratio, have approximately a mirror-image relationship, except that the latter curve does not level off even at the highest clay concentrations employed.

The sedimentation volumes continued to increase with decreasing bismuth subnitrate–bentonite weight ratios or increasing bentonite concentrations in the range of compositions where the electrophoretic mobility had reached a rather high and constant negative value, i.e., for Mixtures 6 and 7 and 9–17. This finding is ascribed to the formation of the characteristic thixotropic house-of-cards structure (21) by the excess, free, or nonadsorbed bentonite. This scaffolding is due to the attraction between the positively charged edges and the negatively charged faces of the bentonite platelets (21). It probably incorporates as cornerstones the coarse bismuth subnitrate particles covered with a film of sorbed bentonite.

The viscosity measurements of Fig. 1 are in qualitative agreement with the results of the electrophoresis and sedimentation volume measurements. At infinite and very high bismuth subnitrate–bentonite ratios, the bismuth subnitrate particles have high positive charges and repel one another. Consequently, their suspension is deflocculated and has a low viscosity (19) as well as a small sedimentation volume. As the bismuth subnitrate–bentonite weight ratio decreases and the absolute value of the positive ζ-potential approaches zero, increasing flocculation produces higher viscosities. With further decreases in the weight ratio, as the ζ-potential turns increasingly negative, the bismuth subnitrate particles are peptized and the viscosity drops again. At still lower weight ratios, while the negative ζ-potential levels off because the surface of the bismuth subnitrate particles is saturated with bentonite, the viscosity begins to increase for the same reason that caused continued increases in the sedimentation volume, namely, the excess, nonadsorbed bentonite forms a house-of-cards structure.

The maximum and minimum in the plot of viscosity *versus* the bismuth subnitrate–bentonite weight ratio of Fig. 1 occur at a lower ratio than the one at which the electrophoretic mobility and sedimentation volume *versus* weight ratio plots of Fig. 4 undergo their sharpest changes. The difference may be ascribed to a difference in bismuth subnitrate concentration. The suspensions used to measure viscosities contained twice as much bismuth subnitrate than those used to measure sedimentation volumes.

Caking was relieved by two different mechanisms. At low bentonite

concentrations, between bismuth subnitrate–bentonite weight ratios of approximately 1200 and 230, the sorbed clay reduced the high positive ζ-potential of the bismuth subnitrate particles to zero or to small positive or negative values. In the absence of strong electrostatic repulsion between the bismuth subnitrate particles, they flocculated in suspension and produced large sedimentation volumes. This mechanism is applicable to all finely dispersed colloidal solids of opposite charge; their specific surface area must be much higher than that of the coarse particulate drug.

At higher bentonite concentrations, for bismuth subnitrate–bentonite weight ratios below 230, enough bentonite was present to coat the bismuth subnitrate particles completely with clay platelets. At those levels, the house-of-cards structure of bentonite, which incorporated and thereby agglomerated the bentonite-covered bismuth subnitrate particles, was responsible for preventing those particles from forming compact sediments. This flocculation occurred despite the fact that the clay-coated particles had a negative ζ-potential large enough to prevent flocculation in the absence of nonadsorbed or free bentonite. This mechanism for relieving caking is only operative with finely dispersed colloidal solids of opposite charge that are also capable of producing structural viscosity at low concentrations.

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Urinary Excretion of Probenecid and Its Metabolites in Humans as a Function of Dose

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Abstract □ A GLC assay was used to study the excretion of probenecid and its metabolites in the urine of human subjects following oral doses of 0.5, 1, and 2 g. From 75 to 88% of the dose was found in the urine. The major metabolite, probenecid acyl glucuronide, accounted for 34–47% of the dose. Approximately equal amounts (10–15%) of the mono-N-propyl, secondary alcohol, and carboxylic acid metabolites were excreted in the unconjugated form with only traces in the conjugated form. The primary alcohol metabolite was not found in measurable amounts. The terminal half-lives for excretion of all metabolites were in the range of 4–6 hr, were independent of dose, and were limited by their rates of formation. A prolonged time course of excretion of the metabolites, particularly at higher doses, suggests that probenecid, being poorly soluble in water, precipitates from solution in the GI tract, forming a depot of drug from which absorption is dissolution rate limited. The urinary excretion of unchanged probenecid, which accounts for 4–13% of the dose, is dependent on both the pH and flow rate of urine.

Keyphrases □ Probenecid and metabolites—urinary excretion as a function of dose □ Excretion, urinary—probenecid and metabolites, effect of dose □ Uricosuric agents—probenecid and metabolites, effect of dose □ Metabolism—probenecid, urinary excretion as a function of dose

Probenecid, 4-[(dipropylamino)sulfonyl]benzoic acid, was introduced as an uricosuric agent in 1951. However, only recently has its metabolic fate in humans and animals been fully elucidated (1–4). Studies of the disposition of the drug generally have used ^{14}C-labeled probenecid, and studies in humans have been limited by the need for a convenient nonradioactive assay. A GLC assay of the methyl esters of probenecid and its metabolites was employed for studies in rats (1, 4). The GLC assay of the propyl esters was utilized in the present study of the urinary excretion of probenecid and its metabolites in humans.

The plasma half-life of probenecid has been reported to increase with increasing dose and has been attributed to a decreased rate of metabolism at higher doses (5, 6). Unfortunately, in the human study (5), the determinations of plasma half-lives were not conducted over a sufficiently long period to be certain that distributive equilibrium had been achieved. In the dog study (6), the period over which plasma levels were measured was not indicated. Therefore, it is not clear whether this reported dose-dependent plasma decline of probenecid is real or simply the artifactual result of an inadequate sampling protocol. Therefore, the effect of increasing doses of probenecid on the urinary excretion of the drug and its metabolites in humans was investigated.

EXPERIMENTAL

Method—Unconjugated probenecid and its unconjugated metabolites were extracted with methylene chloride from urine acidified with 5 N HCl, converted to the propyl esters with diazopropane, and quantitated by GLC. A stainless steel column (2.8 mm × 2 m) packed with 10% OV-1 on 80–100-mesh Chromosorb W-HP was used. The gas chromatograph[1] was fitted with a flame-ionization detector. Operating parameters were: column temperature, 250°; injection port temperature, 280°; nitrogen carrier gas flow, 23 ml/min; and sensitivity, 2.5 × 10^{-11} amp full scale. N,N-Dibenzyl-(2,5-dimethylbenzene)sulfonamide was used as the internal standard. Optimum column performance was maintained by occasional injection of a silylating mixture[2] followed by overnight conditioning of the column.

Total drug and metabolites were determined by heating the acidified urine for 2 hr at 100° before extraction, derivatization, and chromatography[3]. Metabolites were synthesized as reported earlier (1, 4).

Protocol—Two healthy male subjects (Subject 1, 27 years, 58 kg; Subject 2, 42 years, 61.4 kg) did not ingest other drugs or alcoholic beverages for 2 days prior and 3 days after ingestion of probenecid. After fasting overnight, the initial morning urine sample was taken for use as an analytical control. Since the absorption of many drugs having poor water solubility is known to be dissolution rate limited, the dose of probenecid (0.5, 1, and 2 g) was administered orally in solution. The drug[4] was dissolved in 200 ml of 2–3% sodium bicarbonate, the minimum quantity required for complete solution. In one case (2-g dose, Subject 2), the dose was dissolved in 200 ml of dilute