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Enhancing Fluidity of Concentrated Antacid Suspensions

ALLEN HEYD [x] and DADI J. DHABHAR

Abstract [] Highly concentrated antacid suspensions can be fluidized by adding a colloidal polyelectrolyte to alter the charge on antacid particles from positive to negative. A deflocculated state is assumed to exist in such preparations, as supported by electrophoretic and viscometric analyses. When viscosity is directly correlated with the ζ-potential, viscometry becomes particularly useful in confirming that the suspension has been maximally fluidized.

Keyphrases [] Antacid suspensions, concentrated—fluidized by addition of colloidal polyelectrolyte, viscosity correlated with ζ-potential, electrophoretic and viscometric measurements [] Fluidized antacid suspensions—preparation using colloidal polyelectrolyte, viscosity correlated with ζ-potential, electrophoretic and viscometric measurements

Table I—Physical Properties of Antacids

Property	Dried Aluminum Hydroxide Gel USP[a]	Magnesium Hydroxide NF[b]	Calcium Carbonate USP[c]
Particle size[d], μm	2.34 (0.28–6.42)[e]	8.12 (1.4–42)	4.39 (0.28–9.2)
Shape	Asymmetric round	Asymmetric round	Barrel shaped
Bulk density, lb/ft^3	19–23	17–25	17

[a] J. T. Baker Chemical Co., Phillipsburg, N.J. [b] Mallinckrodt Chemical Works, Jersey City, N.J. [c] Pfizer Mineral, Pigments and Metals Division, Clifton, N.J. [d] Mean volume diameter. [e] Particle-size range.

Primary goals in formulating stable suspensions of coarse particles are to prevent caking and, thus, to maintain a stable shelflife. Obtaining these objectives becomes particularly difficult when preparations are highly concentrated because the classical techniques of flocculation no longer apply.

Flocculation appears to be the preferred method for preparing coarse suspensions which can be redispersed easily by shaking (1–3). In the phenomenon of flocculation, the force of attraction between particles predominates, causing the particles to form loose aggregates. Should repulsion forces prevail, however, the particles separate or deflocculate, settling slowly. A suspending and/or gelling agent is required to stabilize such a preparation to prevent caking.

In a study of the surface characteristics of particles and the intensity of particle interaction related to the caking of insoluble particles in aqueous dispersion, flocculation was controlled by adding an electrolyte; the resulting product did not cake (4). Martin (5), in reviewing the physicochemical principles applicable to caking and flocculation, emphasized that maximal flocculation occurred within a range of low positive to low negative ζ-potential. Deflocculation and caking occurred at either extreme, e.g., high positive or high negative (Fig. 1). Haines and Martin (6), in studying the electrokinetic behavior of insoluble drug parti-cles, correlated the magnitude of the ζ-potential, as calculated from electrophoresis data, with the tendency to cake.

Flocculation technology evolved from research performed on suspensions containing no more than 10% solids. Thus, current flocculation technology did not seem applicable to the preparation of coarse suspensions containing, for example, 40% solids. Antacid preparations containing 40% solids do not contain enough free water to achieve a low enough viscosity and easy flow. Furthermore, concentrated suspensions cannot be flocculated to a maximal extent since the potential maximum sedimentation volume on dilution would greatly exceed the original total volume (7).

An alternative to flocculation is fluidization. An elegant system was described for a superior barium sulfate suspension used as a diagnostic contrast medium (8). The use of radiographic techniques to evaluate the in vivo performance of the system was also described (8). In addition, Brown (9) referred to increased fluidity in the preparation of highly concentrated, gelating, antacid systems.

In an investigation of this system (8, 9), the fluidization technique was evaluated. Highly concentrated antacid suspensions of high fluidity (e.g., marked flowability and low viscosity) can be successfully pre-
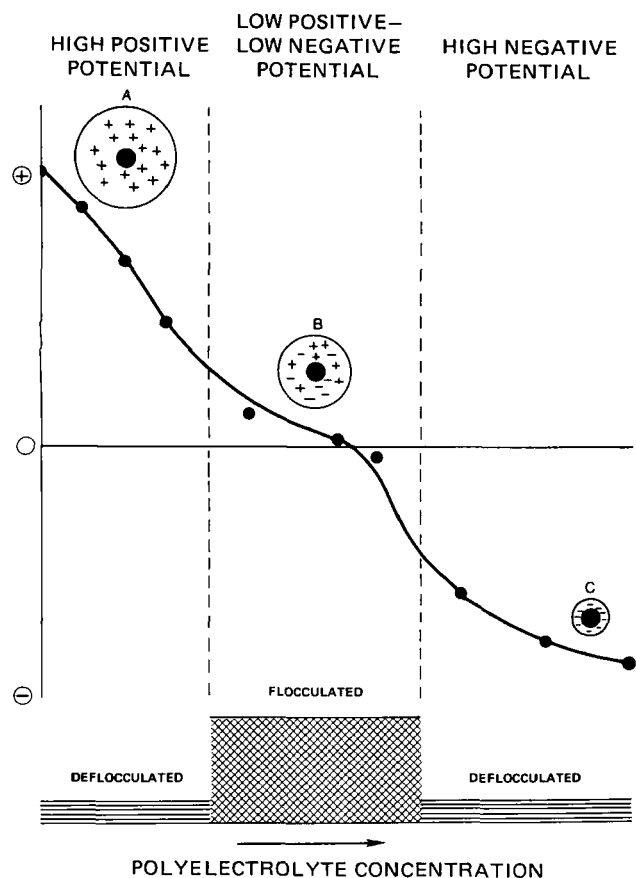
Figure 1—*Schematic diagram depicting deflocculation, which occurs at a high positive or high negative ζ-potential; flocculation occurs at a low positive or low negative ζ-potential. Antacid particle hydration is shown as a function of the ζ-potential. Key: A, high positive (high hydration); B, low positive–low negative (medium hydration); and C, high negative (low hydration).*

pared by this technique using a low molecular weight, colloidal polyelectrolyte as a "fluidizing" agent.

Theoretically, in this system (8, 10) the negatively charged colloidal polyelectrolyte would selectively adsorb onto the surfaces of insoluble particles, such as antacid particles, and deflocculate them once the ζ-potential exceeds the critical value. The purposes of this study were: (a) to determine whether such concentrated suspensions can, in fact, be fluidized; (b) to determine whether electrophoresis can be utilized to follow the degree of fluidization; and (c) to correlate ζ-potential results with viscosity data.

EXPERIMENTAL

Materials—The physical characteristics of the substances used in preparing two antacid suspensions are listed in Table I. Carrageenan sodium[1] of low molecular weight (8000–10,000) served as the negatively charged colloidal polyelectrolyte in each instance.

Aluminum Hydroxide Suspension (25%)—For viscosity measurements, a 25% dispersion of aluminum hydroxide was prepared. The concentration of carrageenan sodium was increased stepwise from 0.2 to 3.2% in seven replicate samples intended for viscosity determinations. Because its small particle size produces a good suspension and allows unhindered movement in the electrophoresis cell, a 0.025% dispersion of aluminum hydroxide served as a
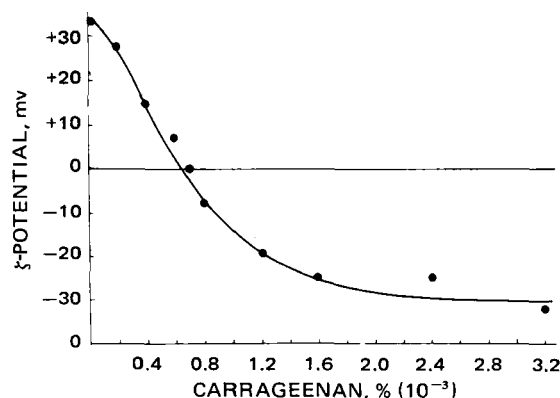
[1] Marine Colloids Inc., Springfield, N.J.

Figure 2—*ζ-Potential of aluminum hydroxide as a function of carrageenan concentration.*

model for the initial measurements of the ζ-potential. It was assumed that this dilution from a 25% dispersion would not alter the equilibrium between the electrolyte and solids and thereby affect the results from a practical standpoint. Concentrations of carrageenan sodium added to the 0.025% suspension were increased stepwise from 0.0002 to 0.0032% in seven replicate samples to determine the effect of a negatively charged colloidal polyelectrolyte upon the ζ-potential of aluminum hydroxide.

Antacid Mixture (38%)—A prototype antacid mixture (38% suspension) was prepared consisting of magnesium hydroxide, dried aluminum hydroxide gel, and calcium carbonate (1:2:6). The content of carrageenan sodium was increased stepwise from 0.2 to 3.2% in eight replicate samples intended for viscosity determinations. The relatively large size of the magnesium hydroxide and calcium hydroxide particles did not permit accurate electrophoretic measurements so the ζ-potential could not be calculated.

Measuring ζ-Potential—Samples of the aluminum hydroxide preparation containing graded amounts of polyelectrolyte were placed in an electrophoresis cell[2] having a molybdenum anode and a platinum cathode. The setting was 150 v. Particles were tracked on a stereoscope[3] using an 8× objective. The ζ-potential was calculated from electrophoretic mobility (EM) data using a standard conversion formula (9):

$$\text{absolute EM} = \frac{(\mu m/\text{sec})}{(v/\text{cm})} = \frac{(\mu m)(\text{cm})}{(v)(\text{sec})} \qquad \text{(Eq. 1)}$$

The mobility of charged particles (expressed in micrometers) was determined from their tracking length as seen in a full-scale 8× ocular micrometer. The time required to traverse 1 full-scale μm division was measured in seconds, v represented the voltage applied, and the distance between electrophoresis cell ports was measured in centimeters.

Measuring Viscosity—Viscosity was determined with a viscometer[4] mounted on a helipath stand. T-bar spindles were used in obtaining measurements of the 25% aluminum hydroxide suspension, while standard round spindles were employed in testing the 38% antacid mixture. The effect upon viscosity resulting from controlling the surface potential of suspended particles with carrageenan could not be determined in the presence of a suspending or gelling agent because the latter "dampened out" the fluidizing action of a polyelectrolyte. However, carrageenan sodium in the low molecular weight range used did not contribute to viscosity.

RESULTS AND DISCUSSION

In the aluminum hydroxide suspension, a change in the ζ-potential was associated with increasing concentrations of carrageenan sodium (Fig. 2). This negatively charged, hydrophilic, colloidal polyelectrolyte reduced the positive charge, causing a rapid fall in the ζ-potential. A negative ζ-potential was reached at $0.7 \times 10^{-3}\%$ carrageenan concentration.

Maximum fluidization was achieved at approximately 1.6 ×

[2] Riddick Type II UVA, Riddick Zeta Meter Inc., New York, N.Y.
[3] Zeta Meter.
[4] Model LVT-5x, Brookfield Engineering Laboratories, Stoughton, Mass.
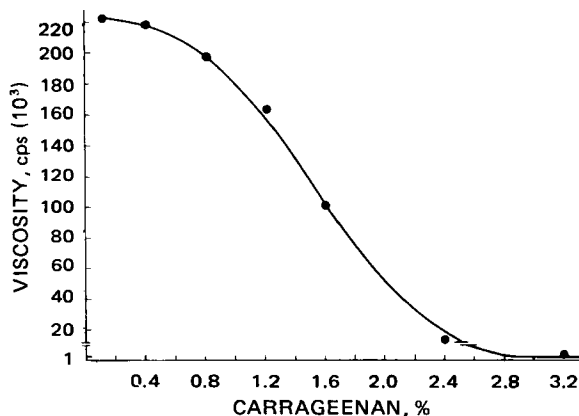
Figure 3—*Viscosity of aluminum hydroxide in water as a function of carrageenan concentration.*

Figure 4—*Viscosity of an antacid mixture in water as a function of carrageenan concentration.*

10^{-3}% colloid, as evidenced by a plateau in the ζ-potential and as confirmed with viscosity data. Higher concentrations produced no further change. The ζ-potential curve indicates that the aluminum hydroxide particles acquired a negative charge, corresponding to a negative ζ-potential, which was great enough to surpass the critical value and thus become deflocculated (5). If deflocculation occurs, then it is the mechanism by which fluidization is achieved.

Viscosity of the 25% aluminum hydroxide suspension decreased as the carrageenan concentration increased (Fig. 3). A plateau in viscosity occurred at about 2.4% colloid. Initially, the viscosity of the 25% suspension was approximately 220,000 cps; this preparation had a light paste-like consistency and did not pour. After 3.2% carrageenan was added, the viscosity decreased to approximately 1000 cps; the suspension poured easily from a narrow-necked bottle. An inverse correlation is apparent between colloid concentration and viscosity (Fig. 3) as well as ζ-potential (Fig. 2).

Similarly, the viscosity of the 38% antacid mixture decreased with increasing amounts of carrageenan (Fig. 4). Initially, the viscosity of the mixture was about 1900 cps; it had a thick, lotion-like consistency. Viscosity began to approach the plateau at a concentration of 1.2% carrageenan; and at a concentration of 2.0% carrageenan, the viscosity reached a plateau. This preparation was a thin, smooth liquid which poured easily from a narrow-necked bottle. This change correlated closely with the change in the ζ-potential (Fig. 2).

When comparing viscosity data (Figs. 3 and 4) with ζ-potential values (Fig. 2), it appears that in both antacid systems the decrease in viscosity following the addition of a colloidal polyelectrolyte is correlated with a change from a positive to a negative ζ-potential. Viscometry, therefore, becomes a simple and practical replacement for ζ-potential determinations in this and similar systems. Viscometry can be particularly important when establishing a condition of maximal or optimal fluidization during the large-scale manufacture of antacid suspensions.

These data demonstrate that fluidity of a concentrated antacid mixture can be achieved by using a colloidal polyelectrolyte (fluidizer) such as low molecular weight carrageenan sodium. The mechanism appears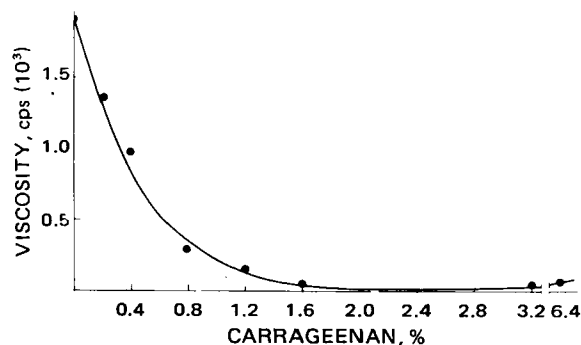 to be that the fluidizing agent—electronegatively charged—selectively adsorbs onto the positively charged antacid particles, deflocculating them (Fig. 1). Such adsorption imparts an electronegative charge (as measured by the ζ-potential) onto the antacid particles, decreasing the demand for water. In effect, particles become *dehydrated* relative to their earlier electropositive hydrated state (11).

The Derjaguin–Landau–Verwey–Overbeek theory, which describes the role of electrolytes in flocculation, is another possible explanation for the fluidization phenomenon. This theory has been reviewed frequently (1–4) and can be used to describe the concept of less water being associated with the antacid particles. As a result, a greater number of particles may be suspended in a given volume of water, thus enhancing the fluidity of the preparation. This fluidized suspension of low viscosity can then be made physically stable by incorporating suitable suspending and/or gelling agents.

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