

Figure 3—Cumulative urinary excretion of (R)-(-)-[²H₃]methadone and (S)-(+)-[²H₃]methadone determined in Patient 1.

enantiomers. Data presented in Fig. 3 illustrate the cumulative urinary excretion of the two methadone enantiomers in Patient 1. (S)-(+)-methadone reaches a cumulative excretion plateau value of 5.2% by 120 hr. In contrast, the (R)-(-)-methadone continues to be excreted throughout the study; by 168 hr, 9.8% of the dose was excreted as the unmetabolized drug. The urinary data, together with the plasma drug level data, suggest a differential renal clearance mechanism for the excretion of the unchanged methadone enantiomers. Full assessment of each step of the disposition of the separate enantiomers of methadone and its metabolites, including hepatic uptake metabolism, biliary excretion, fecal excretion, and urinary clearance, is needed before the mechanisms underlying the observed differences in overall disposition can be evaluated (25).

REFERENCES

- (1) V. P. Dole, M. E. Nyswander, and M. J. Kreek, *Arch. Intern. Med.*, **118**, 304 (1966).
- (2) M. J. Kreek, "Heroin Dependency: Medical, Economic and Social Aspects," Stratton Intercontinental Medical Book Corp., New York, N.Y., 1975, p. 232.
- (3) B. A. Judson, W. H. Horns, and A. Goldstein, *Clin. Pharmacol. Ther.*, **20**, 445 (1976).
- (4) G. D. Olsen, H. A. Wendel, J. D. Livermore, R. M. Leger, R. K. Lynn, and N. Gerber, *ibid.*, **21**, 147 (1977).
- (5) H. R. Sullivan, S. E. Smits, S. L. Due, R. E. Booher, and R. E. McMahon, *Life Sci.*, **11**, 1093 (1972).
- (6) N. A. Ingoglia and V. P. Dole, *J. Pharmacol. Exp. Ther.*, **175**, 84 (1970).
- (7) A. Goldstein, L. I. Lowney, and B. K. Pal, *Proc. Natl. Acad. Sci.*

USA, **68**, 1742 (1971).

- (8) A. L. Misra and S. J. Mulé, *Nature*, **241**, 281 (1973).
- (9) S. E. Smits and M. D. Myer, *Res. Commun. Chem. Pathol.*, **7**, 651 (1974).
- (10) H. R. Sullivan, S. L. Due, and R. E. McMahon, *J. Pharm. Pharmacol.*, **27**, 728 (1975).
- (11) C. B. Pert and S. H. Snyder, *Science*, **170**, 1011 (1973).
- (12) E. J. Simon, J. M. Miller, and I. Edelman, *Proc. Natl. Acad. Sci. USA*, **70**, 1947 (1973).
- (13) M. J. Kreek, D. L. Hachey, and P. D. Klein, *Life Sci.*, **24**, 925 (1979).
- (14) A. Pohland, H. E. Boaz, and H. R. Sullivan, *J. Med. Chem.*, **14**, 194 (1971).
- (15) E. R. Klein and P. D. Klein, *Biomed. Mass Spectrom.*, **5**, 91 (1978).
- (16) *Ibid.*, **5**, 321 (1978).
- (17) H. R. Sullivan, F. J. Marshall, R. E. McMahon, E. Anggaard, L. M. Gunne, and J. H. Holmstrand, *Biomed. Mass Spectrom.*, **2**, 197 (1975).
- (18) D. L. Hachey, M. J. Kreek, and D. H. Mattson, *J. Pharm. Sci.*, **66**, 1579, (1977).
- (19) M. J. Kreek, C. L. Gutjahr, J. W. Garfield, D. V. Bowen, and F. H. Field, *Ann. N.Y. Acad. Sci.*, **281**, 350 (1976).
- (20) D. A. Knowlton, A. F. Fentiman, and R. J. Foltz, "Research Report to the National Institute on Drug Abuse," Battelle Columbus Laboratories, Columbus, Ohio, Dec. 1, 1978.
- (21) J. I. Brauman, *Anal. Chem.*, **38**, 607 (1966).
- (22) D. L. Hachey, J. C. Blais, and P. D. Klein, *ibid.*, **52**, 1131 (1980).
- (23) M. Berman and M. F. Weiss, "SAAM 27 Users Manual," Department of Health, Education and Welfare Publication Number (NIH) 78-180, U.S. Government Printing Office, Washington, DC 20402.
- (24) D. J. Jenden, M. Roch, and R. A. Booth, *Anal. Biochem.*, **55**, 438 (1973).
- (25) H. R. Sullivan and S. L. Due, *J. Med. Chem.*, **16**, 909 (1973).

ACKNOWLEDGMENTS

Supported by the U.S. Department of Energy through Contract W-31-109-ENG-38, National Institute on Drug Abuse Grant DA-01138, and National Institutes of Health General Clinical Research Center Grant RR-00102. Publication of this manuscript was supported in part by the Children's Nutrition Research Center, SEA, USDA, the Department of Pediatrics, Baylor College of Medicine, and Texas Children's Hospital.

M. J. Kreek was the recipient of a Research Scientist Award (DA-00049) from the NIDA.

The authors acknowledge the support of D. K. Murayama, Director of Central Research Laboratories, Sankyo Co., Tokyo, Japan, given to K. Nakamura during his stay at Argonne National Laboratory.

Effect of Surface Charge and Particle Size on Gel Structure of Aluminum Hydroxycarbonate Gel

JOSEPH R. FELDKAMP *, JOE L. WHITE *, and STANLEY L. HEM **

Received March 6, 1981, from the *Department of Agronomy and the †Department of Industrial and Physical Pharmacy, Purdue University, West Lafayette, IN 47907. Accepted for publication May 14, 1981.

Abstract □ The effect of surface charge and particle size on the gel structure of aluminum hydroxycarbonate gel was studied through the use of a specially designed tension cell. Surface charge has a major effect on the coefficient of bulk compressibility. The charged state is more compressible at lower tensions while the neutral gel is more compressible at higher tensions. In addition, physical properties of gels having a small particle size are more profoundly influenced by interparticle forces than are gels consisting of larger particles. The effect of surface charge and

particle size on gel structure is applied to physical properties such as viscosity and dewatering.

Keyphrases □ Aluminum hydroxycarbonate gel—gel structure, effect of surface charge and particle size □ Gels—aluminum hydroxycarbonate, effect of surface charge and particle size on structure □ Physicochemistry—effect of surface charge and particle size on gel structure of aluminum hydroxycarbonate gel

Investigation of the structure of aluminum hydroxide gel at an atomic level has led to improved understanding of the arrangement of atoms and the types of bonds

present in the various materials collectively known as aluminum hydroxide (1–4). An equally important type of structure, gel structure, which deals with the manner in

which the aluminum hydroxide particles are arranged in space, has not been as extensively studied. For this reason, a series of studies was initiated utilizing a specially designed tension cell to elucidate various relationships between gel structure and physical properties. The role of surface charge and particle size in determining the gel structure of aluminum hydroxycarbonate gel was examined in this study.

BACKGROUND

The tension cell was designed for the study of the gel structure of aluminum hydroxide (5) and was developed from experimental methods used to study clays and related porous materials (6). The tension cell was used to measure the coefficient of bulk compressibility for two aluminum hydroxycarbonate gels having a pH-dependent surface charge and a substantially different particle size.

The coefficient of bulk compressibility, α , is used by soil physicists to describe the degree of consolidation of a solid particle or colloidal matrix on the application of an external load or stress and is typically defined as (7, 8):

$$\alpha = -\frac{1}{V} \frac{dV}{d\sigma} \quad (\text{Eq. 1})$$

where σ represents an applied stress and V is the volume of the system, including both the particle volume and the pore volume. When the tension cell is used, the stress is supplied by applying a small negative pressure or tension, τ . Since the cross-sectional area of the tension cell chamber is constant, the coefficient of bulk compressibility may be expressed in terms of L , the length of the column of gel in the tension cell, and the applied tension:

$$\alpha = -\frac{1}{L} \frac{dL}{d\tau} \quad (\text{Eq. 2})$$

The coefficient of bulk compressibility may be readily calculated if an empirical relationship between the applied tension and the corresponding length of the column at equilibrium can be established. Such a relationship may be obtained through trial and error testing of various mathematical relationships. A particularly successful equation is:

$$L = A(e^{-\beta\tau} + B) \quad (\text{Eq. 3})$$

where A , B , and β are constants adjusted to best fit the (τ, L) data pairs. Upon determining the proper empirical form, the coefficient of bulk compressibility is calculated by substituting Eq. 3 into Eq. 2.

EXPERIMENTAL

Two aluminum hydroxycarbonate gels were obtained commercially, and the coefficient of bulk compressibility was determined with the tension cell following dilution to 9.3% equivalent aluminum oxide.

The zero point of charge (ZPC), the pH at which the net surface charge is zero, is an important property of colloidal systems that possess a pH-dependent surface charge. At this pH, the densities of the positive and negative charges are equal (9). The zero point of charge of aluminum hydroxycarbonate gels 1 and 2 was determined to be 6.34 and 7.60, respectively, by a titration procedure (10). The desired surface charge was obtained through adjustment of the pH relative to the zero point of charge by the addition of small quantities of hydrochloric acid or sodium hydroxide to produce a positive, neutral, or negative surface charge. Aluminum hydroxycarbonate gel 1 was adjusted to pH 5.70, 6.34, and 7.40; gel 2 was adjusted to pH 5.50 and 7.00.

The rate of acid neutralization was determined by pH-stat titration at pH 3 and 25° (11).

The relative particle size of the two aluminum hydroxycarbonate gels was determined by measuring the rate of sedimentation of 100 ml of a 1% (w/v) dilution of each gel in a 100-ml graduated cylinder following pH adjustment to equal the zero point of charge. The sedimentation rate is expressed as t_{50} , the time required to settle halfway from the initial height in the 100-ml cylinder to the equilibrium sediment height.

The previously described tension cell procedure (5) was used to determine the equilibrium water outflow as a result of applied tensions up to 15 cm of water. Two modifications were made in the tension cell apparatus to provide more convenient and precise measurements. Since the gel undergoes a decrease in volume due to the outflow of water, the applied tension will decrease during the experiment. This undesirable

effect was previously minimized through the manual readjustment of the height of the tension cell chamber by 0.05 cm for every 1.5 ml of water outflow so that the applied tension remained essentially constant.

This procedure was replaced with a digital motor-drive system, which readjusted the tension on sensing a downward movement of the upper gel surface. The motor triggering mechanism consisted of a pair of platinum electrodes sealed in glass tubing, which were positioned to contact the gel surface. As long as the electrodes contacted the surface, a very small dc current ($<0.1 \mu\text{amp}$) moved through the completed circuit. As outflow of water from the gel proceeded, the gel surface dropped below the electrodes, interrupting the current and activating the digital motor-drive system. The sample chamber was raised to reestablish contact between the electrodes and the gel surface. This apparatus maintained the applied tension within 0.03 cm. A vernier system was attached to the digital motor drive so the accumulated height changes of the tension cell chamber could be measured. At each tension level setting, the overall displacement of the tension cell was equal to the length change of the gel column.

A second modification was made to record automatically the water outflow as a function of time. Water flowed dropwise from the outlet tube and entered a small volumetric flask, which was fitted with a cover having a capillary opening. The flask rested on a weighing pan, which was displaced linearly according to the amount of water in the flask. The downward movement of the weighing pan was monitored with a linear variable differential transformer whose output was continuously recorded. Thus, the equilibrium outflow of water at a particular tension could be easily determined. Equilibrium times ranged from 8 to 48 hr. In every case, the equilibrium outflow of water was equal to the volume change of the gel.

RESULTS AND DISCUSSION

The applied tension is related to the amount of work required, per mole of water, $\Delta\bar{G}_{\text{H}_2\text{O}}$, to remove water from the system (12):

$$\Delta\bar{G}_{\text{H}_2\text{O}} = -\rho g \bar{V} \tau \quad (\text{Eq. 4})$$

where ρ is the density of water, \bar{V} is the molar volume of water, and g is the acceleration due to gravity. To remove $dn_{\text{H}_2\text{O}}$ moles of water from the system requires that an amount of work equal to δW be done on the system:

$$\delta W = \Delta\bar{G}_{\text{H}_2\text{O}} dn_{\text{H}_2\text{O}} \quad (\text{Eq. 5})$$

Equation 5 may be rewritten with the aid of Eq. 4 to give:

$$\delta W = -\rho g \tau A dL \quad (\text{Eq. 6})$$

where A is the area of the tension cell chamber and dL represents a small displacement of the length of the gel column. The work of compression, δW , is expended against the efforts of the gel to retain its original particle arrangement or gel structure. A large work of compression implies either that cohesive forces (van der Waals) are present, tending to prevent the distortion of the particles into a smaller space, or that interparticle repulsive forces (coulombic) are present, which resist a closer approach of particle surfaces.

Although the work of compression is a macroscopic concept, it is ultimately tied to phenomena occurring on a microscopic scale. As illustrated in Fig. 1, each particle may be viewed as residing in a potential well, the depth and width of which are controlled by interparticle force fields. Movement of any particle along some trajectory from one well to another requires that the particle attain sufficient energy to pass over the interposed barrier. If thermal energy is insufficient, there is no appreciable translational motion and the system gels. In such cases, the necessary energy may be provided by applying an external stress such as shear or, in this case, a pressure gradient (tension). The extent to which particles are free to move under an applied external stress is directly dependent on the nature of adjacent energy barriers.

The work of compression is further illustrated in Fig. 2 (A and B) by the shaded regions that are proportional to the work of compression required to displace the gel from a length of 4.5–4.0 cm. The work required to compress the neutral aluminum hydroxycarbonate gel over this range is approximately twice that required to compress the charged aluminum hydroxycarbonate gel, indicating that cohesive forces present in the neutral gel tend to prevent the movement of the particles to a greater extent than the repulsive forces present in the positively charged system.

It is clear that Eq. 3 is a suitable mathematical expression to describe the tension *versus* gel column length relationship since the solid lines

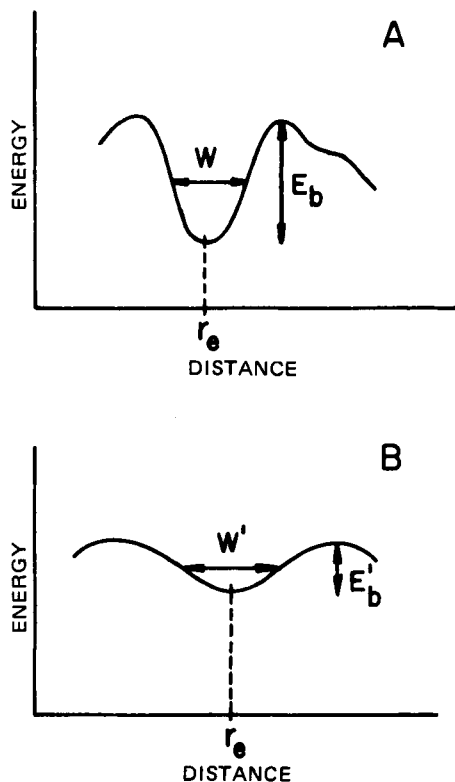


Figure 1—Energy–distance profiles. Key: A, high particle density gel; B, low particle density gel; E_b , depth of the potential well; W , characteristic width of the potential well; and r_e , equilibrium position of the particle.

representing the fitted equation coincide with the data points. Thus, the data in Fig. 2 were used to calculate the compressibility curves shown in Fig. 3.

The coefficient of bulk compressibility of aluminum hydroxycarbonate gel 1 is clearly affected by the presence of surface charge (Fig. 3, A and B). At tension levels less than ~ 9 cm, the positively charged system was considerably more compressible than the neutral gel. This result is similar to the previously observed effect of surface charge on the viscosity of aluminum hydroxycarbonate gel in which the maximum viscosity occurred when the pH equaled the zero point of charge (10).

The underlying mechanism explaining both phenomena is that when

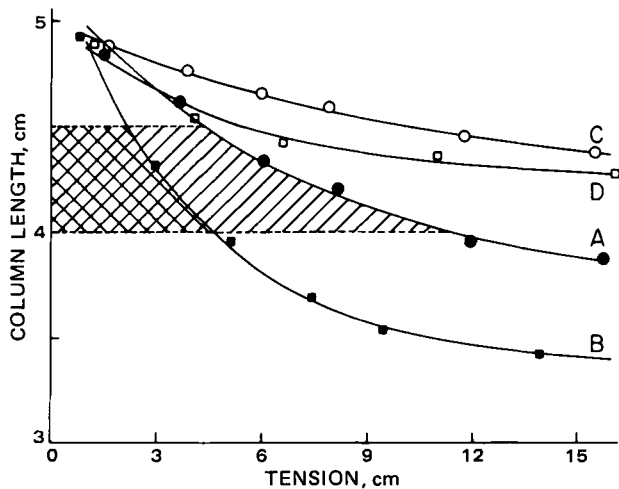


Figure 2—Change in the column length as a result of applied tension. Shaded areas indicate the relative work of compression required to displace aluminum hydroxycarbonate gels 1 and 2 from a length of 4.5 to 4.0 cm. Key: A, gel 1 at pH 6.34 (ZPC = 6.34); B, gel 1 at pH 5.7; C, gel 2 at pH 7.0 (ZPC = 7.60); D, gel 2 at pH 5.5; data points are from tension cell experiments and the solid lines were obtained by fitting Eq. 3 to the data points.

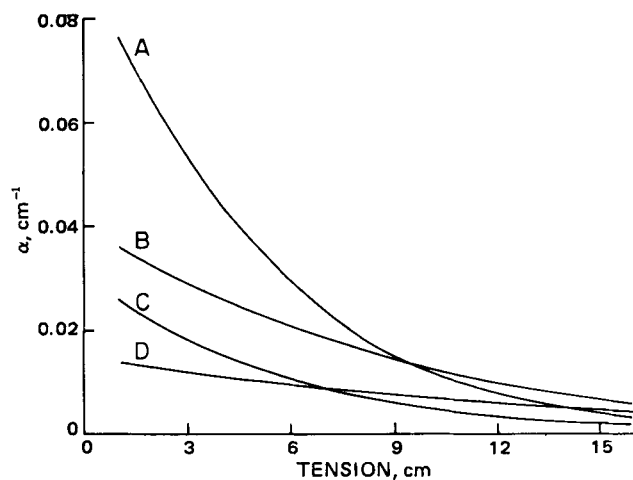


Figure 3—Effect of tension on the coefficient of bulk compressibility, α . Key: A, gel 1 at pH 6.34 (ZPC = 6.34); B, gel 1 at pH 5.7; C, gel 2 at pH 7.0 (ZPC = 7.60); and D, gel 2 at pH 5.5.

sufficient coulombic repulsion is developed to overcome van der Waals attractive forces, the particles are free to move in a less restricted manner. Particles are considered to be more free or mobile under the influence of repulsion than attraction since repelling particles tend to utilize the entire space of the system, whereas attractive forces usually produce structures that confine the particles to rigid, linear chains so that considerable unused space exists (13). Since the charged particles are not so severely confined in space, consolidation of the colloidal matrix in response to water removal may readily take place, leading to a more compressed system. In addition, the absence of attractive forces tending to lock the particles into position permits shear rather easily. At the zero point of charge, however, substantial cohesive forces (van der Waals) resist distortion of the gel structure to form some new structural arrangement.

However, as seen in Fig. 3 (A and B) the charged gel was less compressible than the neutral gel when the applied tension exceeded 9 cm of water. This is a consequence of the initial freedom of movement of the charged particles during consolidation and leads to a more efficiently packed collection of particles. This dense collection of particles is able to resist further compaction more effectively than the neutral gel due to the substantially increased level of coulombic repulsion. In addition, when the aluminum hydroxycarbonate gel is at the zero point of charge, the initial randomness or disorder of the gel structure is locked into place by van der Waals cohesive forces, preventing the formation of an efficiently packed particle network. Consequently, the compressibility of the neutral gel is greater than that of the charged gel at high tensions.

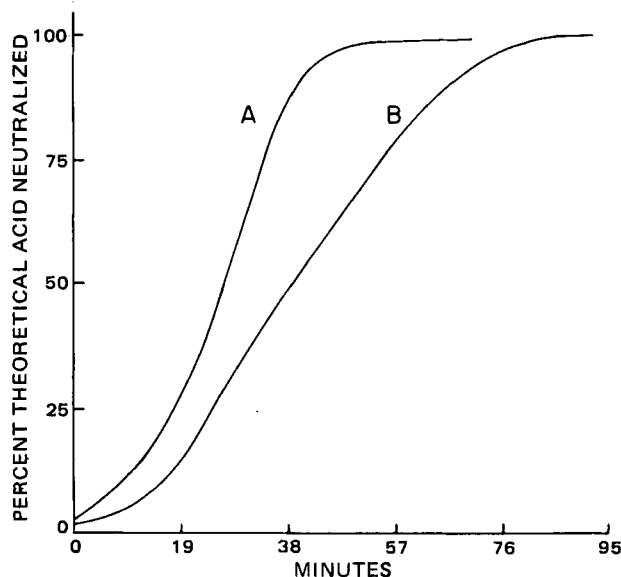


Figure 4—Rate of acid neutralization at pH 3.0 and 25°. Key: A, gel 1; and B, gel 2.

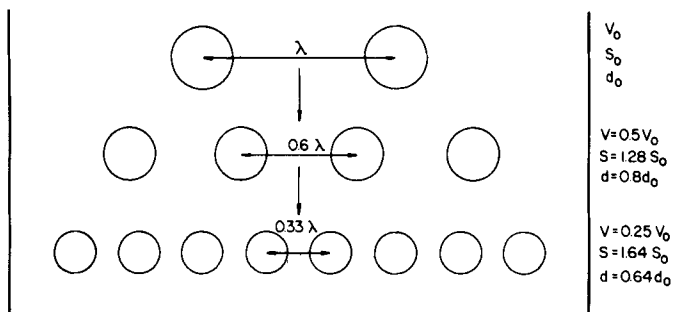


Figure 5—Effect of particle density on interparticle distance. Key: λ , interparticle distance; V , volume of each particle; S , total surface area; and d , diameter of each particle. The volume of each particle is reduced by 50% in each step while the total volume of the particles is constant.

A practical consequence of this behavior is that the charged state permits more convenient water removal, but only when the water content is below that corresponding to a tension of 9 cm of water. Above 9-cm water tension, the neutral state is more desirable for operations involving water removal.

The zero point of charge of gel 2 was 7.6. This gel is believed to have a smaller particle size and, therefore, a greater surface area than gel 1 since this gel became too viscous to mix as the pH was brought to the zero point of charge. It was not possible to adjust the pH to 7.6 where the maximum viscosity occurs because of the high viscosity. This behavior is in contrast to that of gel 1, which became more viscous as the pH was adjusted to its zero point of charge but still remained fluid at the zero point of charge.

The smaller particle size of gel 2 was confirmed by comparing the rate of settling of 1% equivalent aluminum oxide dilutions of gels 1 and 2. The t_{50} value for the sedimentation of gel 1 was 1.8 hr while gel 2 required 4.3 hr for an equivalent degree of sedimentation. The more rapid rate of acid neutralization by gel 2 at pH 3 (where both aluminum hydroxycarbonate gels will be highly charged) also reflects its smaller particle size (Fig. 4).

It was not possible to repeat exactly the tension cell experiment for gel 2 since the viscosity was too great at the zero point of charge. However, the effect of charge on the gel 2 structure was similar to that observed for gel 1 (Fig. 2, C and D). Gel 2 was more compressible when in a highly charged state, *i.e.*, at pH 5.5, up to a tension of ~ 7 cm of water (Fig. 3, C and D). The less charged state, *i.e.*, at pH 7.0, was more compressible at higher tension levels. The point at which the charged gel became more compressible than the neutral gel (7 cm of water) occurred at a lower tension than was observed for gel 1 due to the much greater charge on gel 2.

The most striking difference between gels 1 and 2 was that gel 2 was less compressible regardless of its charge. Since the same types of forces are present in both gels and each gel has the same equivalent aluminum oxide content, the factor responsible for the difference in behavior must be the smaller particle size and, consequently, the greater surface area of 2. Reducing the particle size while maintaining a constant solids concentration will cause gel 2 to have a higher particle density.

The effect of particle density may be illustrated by the example provided in Fig. 5 in which individual particle volume is sequentially halved in a one-dimensional arrangement of particles. Such a system is especially relevant since linear chains are frequently formed under the influence of van der Waals attractive forces (13). Although surface area does not increase substantially upon two subdivisions, the average interparticle distance decreases significantly. Consequently, a gel having a smaller particle size is much more likely to form an extended chain-like network when cohesive interparticle forces exist.

The effect of particle density for the general case of three-dimensional particle arrays with either attractive or repulsive interparticle forces present may be further clarified through the microscopic energy-distance profiles of Fig. 1 (A and B). As was shown, a higher particle density leads to a smaller average interparticle separation distance. Since forces depend inversely on separation distance, the net restoring force exerted on a given particle by all others during a small displacement of the particle from its equilibrium position is greater (as in Fig. 1A). A low particle density yields the opposite effects (as in Fig. 1B) so that particles are less influenced by one another and are not held as tightly in place. This conclusion follows for coulombic-type forces as well as van der Waals forces so that gel 2 is predicted to be less compressible than gel 1 in both its charged and discharged states. The experimental results observed in Fig. 3 support this conclusion.

REFERENCES

- (1) S. L. Nail, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **65**, 1188 (1976).
- (2) J. L. White and S. L. Hem, *ibid.*, **64**, 468 (1975).
- (3) C. J. Serna, J. L. White, and S. L. Hem, *Soil Sci. Soc. Am. Proc.*, **41**, 1009 (1977).
- (4) C. J. Serna, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **67**, 1144 (1978).
- (5) E. A. Lipka, J. R. Feldkamp, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, in press.
- (6) D. Swartzendruber, in "The Flow of Water in Unsaturated Solids," R. J. M. DeWeist, Ed., Academic, New York, N.Y., 1969, chap. 6.
- (7) J. Bear, "Dynamics of Fluids in Porous Media," American Elsevier, New York, N.Y., 1972, pp. 52-56.
- (8) E. H. Davis and G. P. Raymond, *Geotechnique*, **15**, 161 (1965).
- (9) R. G. Gast, in "Minerals in Soil Environments," J. B. Dixon and S. B. Weed, Eds., Soil Science Society of America, Madison, Wis., 1977, pp. 27-73.
- (10) J. R. Feldkamp, D. N. Shah, S. L. Meyer, J. L. White, and S. L. Hem, *J. Pharm. Sci.*, **70**, 638 (1981).
- (11) N. J. Kerkhof, R. K. Vanderlaan, J. L. White, and S. L. Hem, *ibid.*, **66**, 1528 (1977).
- (12) P. F. Low, *Soil Sci.*, **93**, 6 (1962).
- (13) J. Mahanty and B. W. Ninham, "Dispersion Forces," Academic, New York, N.Y., 1976, pp. 21, 22.

ACKNOWLEDGMENTS

Supported in part by William H. Rorer, Inc.
This report is Journal Paper 8456, Purdue University Agricultural Experiment Station, West Lafayette, IN 47907.