DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(11), 1285-1302 (1995)

PHYSICOCHEMICAL CHARACTERISTICS OF COMMERCIAL ALUMINUM HYDROXYCARBONATE GELS.

René D. Peralta Rodríguez*[1], Claudia T. Saucedo Salazar[2], Isabel C. Valdés Silva[2].

[1]Centro de Investigación en Química Aplicada, Blvd. Ing. Enrique Reyna H. No. 140, C.P. 25100, Saltillo, Coahuila, México.

[2]Química y Farmacia, S.A. de C.V., Av. Manuel Acuña No. 100, C.P. 25900 Ramos Arizpe, Coahuila, México.

ABSTRACT

Four commercial samples of AHC each from different manufacturer or distributor in the USA, Canada and Mexico, were studied to determine particle size distribution, viscosity, rate of settling, pH, point of zero charge (PZC), IR spectra and sodium content. These properties are of interest to the raw material manufacturer, the formulator and the consumer, since they impart desirable characteristics to the finished product. It was found in this work, that the average particle size varied between 3.90 and 2.01 μm with standard deviations of 4.10 μm and 3.99 μm, respectively; the viscosities of 4% (w/w) equivalent $Al(OH)_3$ suspensions, ranged from 49 to 10 mPa.s and the sediment fractions after 24 hours for these suspensions oscillated from 0.44 to 0.59. The pH was between 5.61 and 7.60 and the PZC varied from 6.45 to 7.33. The sodium content found in this work was between 0.0406 and 0.5620 g/L. The infrared spectra obtained for the

---

* To whom correspondence should be addressed.

obtained for the four samples indicated the presence of the absorption bands assigned to carbonates in the range of 1525 and 1518 cm^{-1}, 1440 cm^{-1}, 1104 and 1088 cm^{-1} and 857 to 843 cm^{-1}. These results are discussed from the implications that they have to the manufacturer and to the formulator, including the aesthetics of the finished product.

INTRODUCTION

Aluminum hydroxycarbonate gels (AHC) are important because of their antacid properties used in the treatment of gastrointestinal conditions. Thus, the raw material should have adequate characteristics to facilitate the formulation process and to improve the sensory attributes of the finished product, besides complying with the pharmacopeial specifications. The sensory attributes of a suspension are important since they contribute significantly to the patient acceptance of the drug.

Four useful characteristics of these gels are 1) particle size distribution; 2) viscosity; 3) settling rate and 4) surface charge, defined as the difference between the point of zero charge (PZC) and pH (surface charge = PZC - pH). These characteristics are important to predict rheological behavior and appearance of AHC and of the finished product. Additionally, they provide information that can be applied in the operations of settling and washing of the AHC after precipitation that could contribute to process optimization.

The pH of precipitation of AHC is also of the utmost importance since it will directly affect pH, PZC, sodium content, viscosity, and particle size distribution of the raw material at the end of the process. Also, under certain conditions of pH, it is possible to interchange sodium with magnesium that might come in the water used for washing of the AHC and lower the sodium content of the final gel (1). In another report (2) the same authors point out that it is possible to obtain low-sodium AHC gels when they are precipitated in a pH range between 6.5 and 7.0. From the therapeutics point of view, it is very important the sodium content of AHC containing formulations for patients who present heart conditions in addition to gastrointestinal disorders, since they are limited to low sodium intake. It has been reported (3) that one of four quality criteria for antacid suspensions is that the formulation should provide less than 10% (50 mg) of the daily allowance in a strict sodium-restricted diet, when used in a regime of seven doses per day, each capable to neutralize 40 mEq of acid.

The PZC is defined as the pH in which the net surface charge is zero and has an influence on important physical properties to the AHC manufacturer and to the formulator of antacids. Among these properties are viscosity, settling rate, and ion retention (byproducts during precipitation) in the electrical double-layer of the AHC particle. When the pH approaches the PZC, viscosity increases, reaching a maximum at a pH above the PZC (4). On the other hand, the rate of settling decreases when the pH passes through the PZC. At the point where the pH reaches the PZC, the double layer collapses, the surface charge and the zeta potential are zero, there is no attraction of ions toward the particles, facilitating the washing of the AHC gels and contributing to a better removal of sodium ions.

The pioneering work of Hem and co-workers (5) in 1975 established for the first time, through infrared and Ramman spectroscopy, that the aluminum hydroxide gels used as antacids in the pharmaceutical industry are in fact amorphous aluminum hydroxycarbonates in whose structure the carbonate ion is directly linked to aluminum. The latter has been confirmed by the same group in other reports (6-10). In these works the IR spectra of AHC are compared with those of crystalline forms of aluminum hydroxide, $Al(OH)_3$, which lacks the physicochemical characteristics of the product used as antacid.

In this article, the results of a comparative study of four commercial samples of AHC gels from different manufacturers in North America (USA, Canada and Mexico) are reported. The samples were analyzed to determine particle size distribution, viscosities, settling rates, pH, PZC, sodium content and IR spectra. The results are compared among these samples and with data reported in the literature for AHC. Additionally, the results are discussed regarding their implications during gel manufacturing, formulation, aesthetic attributes of the finished product and the AHC identity determined by IR spectroscopy.

THEORETICAL CONSIDERATIONS

1. Settling Rate.

For a rigid, spherical particle, freely settling in an infinite medium under the action of gravity, the rate of settling is given by Stokes law (11)

$$V = \frac{dx}{dt} = \frac{2r^2g\ (d_1 - d_2)}{9\mu} \qquad \text{Eq. 1}$$

V = settling rate, m/s
x = distance, m
t = time, s
r = particle radius, m
d_1 = particle density, kg/L
d_2 = medium density, kg/L
g = acceleration due to gravity, m/s
μ = medium viscosity, mPa.s

Stokes law assumes that the particle is uniform, it does not causes turbulence during free fall and that there is no particle-fluid interaction. Under these conditions the only force acting on the particle is gravity.

As can be seen from Eq. 1, as particle diameter and the driving force (d_1 - d_2) decreases, the settling rate decreases, which also occurs when the medium viscosity increases. This behavior is useful for the raw material manufacturer and to the formulator of antacid suspensions, as will be discussed later.

The settling rate can be characterized through the volume fraction of sediment, F, defined by (12)

$$F = \frac{V_u}{V_o} \qquad \text{Eq. 2}$$

V_u = solids sediment volume at time t, L
V_o = initial volume of suspension, L

2. Viscosity

Viscosity is an expression of the fluids resistance to flow. The flow properties of a Newtonian liquid are represented in quantifiable terms by (11)

$$\frac{f}{A} = \mu \frac{dv}{dx} \qquad \text{Eq. 3}$$

$\frac{f}{A}$ = force per unit area required to produce flow, N m^{-2}

μ = viscosity coefficient, Pa.s

$\frac{dv}{dx}$ = velocity gradient for flow (the difference between velocity of flow of two planes of liquid separated by an infinitesimal distance), s^{-1}.

According to Eq. 3, viscosity is directly proportional to the force applied to induce flow in the fluid. Suspensions are heterogeneous systems and their rheological behavior is, generally, non-Newtonian, since their flow characteristics depend on the shear rate and the time during which the deformation is applied. Thus, to compare the viscosities of non-Newtonian fluids confidently, viscosity determinations should be carried out applying the same shear rate and for the same length of time. Bird et al. (11) present proposed equations to express the steady-state relation between t and $\frac{dv}{dx}$ for non-Newtonian fluids.

3. The electrical double-layer.

The colloidal model for a particle with net electronegative charge, involves a layer of negative charge surrounded by positive charges (Stern layer) to form the double layer. These positive charges become more diffuse as they move from the particle towards the bulk. Two potentials can be associated with the double layer: the Nernst potential that exists between the shear plane (plane of slip between the double layer and the bulk media) and the solid surface, and the zeta potential which is the potential existing between the shear plane and the bulk phase (13).

It can be shown that for small colloidal particles, with low charge and in the presence of electrolites, with water as the dispersing media at 298 K, the thickness of the double layer can be approximated by

$$d = \frac{2.3 \times 10^{-9}}{i} \qquad \text{Eq. 4}$$

where "d" is the double layer thickness (cm) and "i" is ionic strength (13). As can be seen from Eq. 4, as the ionic strength increases the thickness of the double layer decreases eventually collapsing at high ion concentrations, the net particle surface charge becomes zero and the zeta potential is zero. The pH value at which this condition occurs is known as the point of zero charge (PZC).

MATERIALS AND METHODS

Four commercial samples of AHC, each from a different manufacturer or distributor located in the USA, Canada and Mexico, were studied. The samples were identified as A, B, C, and D. All chemicals used in the tests were either analytic or reagent grade.

1. $Al(OH)_3$ assay.

The determinations of equivalent $Al(OH)_3$ in the AHC samples were carried out using a complexometric technique (14).

2. Particle size distribution.

Particle size distribution was determined in an image analyzer (OMNIMENT II, Buehler, U.S.A.). The samples were prepared diluting one drop of a well-agitated sample of AHC gel in 10 mL of deionized water. A drop of this dilution was taken to be analyzed in the apparatus.

3. Viscosity.

The viscosity was determined in triplicate runs at 25°C in a calibrated Brookfield LVF viscosimeter using spindle No. 2 at 30 rpm. The concentration of the samples was adjusted to 4% (w/w) equivalent $Al(OH)_3$.

4. Settling rate.

The settling rate was determined at 25°C using a suspension containing 4% (w/w) equivalent $Al(OH)_3$ and at the resulting pH of the suspension. 100 mL graduated cylinders were used for this test filling with each suspension up to the mark and taking readings of settled solids volume every hour for 11 hours and then after 22, 23 and 24 hours. The data were plotted as fraction of settled solids volume versus time.

5. Sodium content.

Sodium content was determined using an atomic absorption apparatus (Perkin Elmer 2380) and the sodium content of a typical antacid formulation of 4% (w/w) AHC and 4% (w/w) $Mg(OH)_2$ was calculated for each dose capable to neutralize 40 mEq of acid. The acid neutralizing capacity (mEq/g) was determined as described in the U.S. Pharmacopeia (14).

6. pH

pH determinations were carried out in triplicate at 25°C using a calibrated potentiometer (Model 12, Beckman Instruments).

7. Point of zero charge.

The PZC was determined by the addition of an electrolite (4M KCl) to suspensions of the gels containing 1% (w/w) equivalent Al_2O_3, at 25°C. 100 mL of deionized water were added to 100 mL of each sample. To the diluted sample, 0.5 mL of 4M KCl were added, the mixture was thoroughly stirred for five minutes and the pH was recorded. The addition of KCl was continued up to the point where the pH was constant after four or five additions. With the PZC and pH of the suspension the net surface charge of each gel was calculated.

8. Infrared spectra.

To obtain the IR spectra of each sample, a thin layer of air-dried gel was obtained, following the procedure of Serna et al. (8). The air-dried AHC gel was prepared with spectroscopic grade KBr. The spectra were obtained with an FTIR spectrophotometer (Model 710, Nicolet).

RESULTS AND DISCUSSION

The results obtained for particle size distribution and viscosity are presented in Table 1; settling rates are reported in Fig. 1. It can be seen from this figure that the sediment fractions after 24 hours were 0.44 for AHC gels A and C, 0.50 for gel D and 0.59 for gel B.

As can be observed in Table 1, the sample with greater average particle size was C and it was also the sample with greater settling rate, Fig.1. This fact agrees with Stokes law in which settling rate is directly proportional to particle size. The gel with slowest settling rate was B and although it has greater maximum particle size than the other samples, and small average particle size, Table 1, it was the sample with the smallest standard deviation, that is, it was the sample with the most homogeneous particle size. This situation is shown in the settling rate that, according to Stokes law, should be slower than the one obtained experimentally. Further, from theoretical considerations it is expected that the gel with lowest viscosity would have greater settling rate, as occured

TABLE 1

VISCOSITY AND PARTICLE SIZE DISTRIBUTION OF AHC GELS.

SAMPLE	VISCOSITY, mPa.s	PARTICLE SIZE DISTRIBUTION, μm					
		AVERAGE PARTICLE SIZE ± SD,	MINIMUM SIZE,	MAXIMUM SIZE,	90%	75%	50%
A	13	2.01 ± 3.988	69.08	0.56	<3.1	<1.6	<1.1
B	49	2.04 ± 2.130	90.14	0.56	<3.3	<2.3	<1.6
C	10	3.59 ± 4.103	70.07	1.14	<8.0	<4.6	<2.3*
D	15	3.51 ± 4.503	50.89	0.54	<8.8	<4.4	<2.2

* 42% instead of 50%.

with gel C, and the sample with greater viscosity, B, would have slower settling rate, Fig.1. Sample A has the smallest average particle size although it has a greater standard deviation than gel B; this fact suggests that A was a less homogeneous sample than B. With these results, it would be expected a high viscosity and low settling rate; however, this sample showed a viscosity of 13 mPa.s and higher settling rate than gels D and B. This unexpected behavior according to Stokes law, can be explained by electrostatic attractive interactions among particles that affect their free movement and are strongest when the particles have a slightly negative net surface charge (15), Table 2. This condition would lead to the formation of aggregates that would settle faster than primary or secondary particles.

Sample D presented average particle size greater than samples B and A, but slightly higher viscosity and lower rate of settling than gel A. This behavior can be explained as follows (16): sample D was the most heterogeneous (higher standard deviation) and 67 % of the particles were below the average size. These small particles contribute to increase viscosity and decrease rate of settling.

Results of particle size distribution reported by Liu et al. (15) indicate the presence of primary, secondary and aggregated particles. Secondary particles

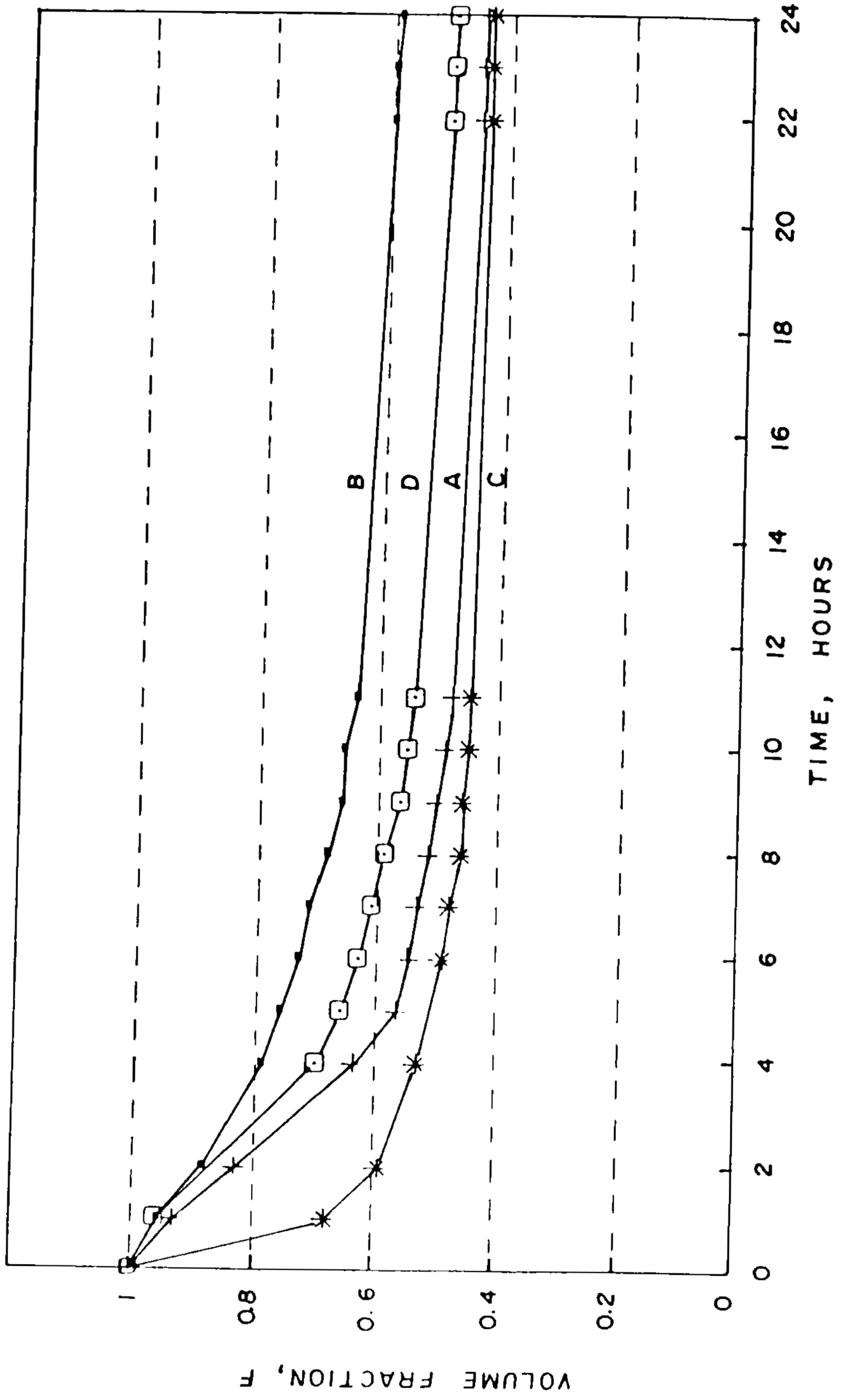

FIGURE 1

Settling rates of AHC gels (4% $Al(OH)_3$)

TABLE 2

pH, POINT OF ZERO CHARGE AND SURFACE CHARGE OF AHC SAMPLES.

SAMPLE	pH	PZC	SURFACE CHARGE
A	6.55	6.45	- 0.10
B	5.61	6.45	+ 0.84
C	7.36	6.98	- 0.38
D	7.60	7.33	- 0.27

are formed by primary particles due to cohesive van der Waals forces whereas aggregates form from secondary particles as the balanced result of attractive and repulsive forces described by the Dejarguin, Landau, Verwey and Overbeeck theory (17). In their research, Liu et al. (15) found that primary particles range in size from 25 to 3700 Å ($25x10^{-4}$ to 0.37 μm), as determined using electron transmission photomicrographs. In the same report, they found for two samples of spray dried AHC, that particles had a size of 14,500 Å for one sample and 27,000 Å for the other. These two values are close to the average particle sizes reported for the four wet gels in this work, although the drying process could modify the particle size. Further, Tempio and Zatz (12) reported for a spray dried sample of AHC suspended in water, a geometric mean of about 10 μm. The measurements were made with an electronic particle counter. The results for the spray dried samples and the four gels reported here suggest that most of the particles were aggregates and not primary particles, besides the limitations of the technique (image analyzer) used in this work to measure particle size.

Colloidal stability of a suspension implies that, for a pharmaceutical preparation, the suspension should not settle or if settled should be easily redispersed within the useful life of the preparation (pharmaceutical stability, (12)). However, from the point of view of acceptance by the consumer, a settled suspension may not be attractive, and formulators seem to favor colloidal stability of antacid suspensions. The results of rate of settling reported here could be

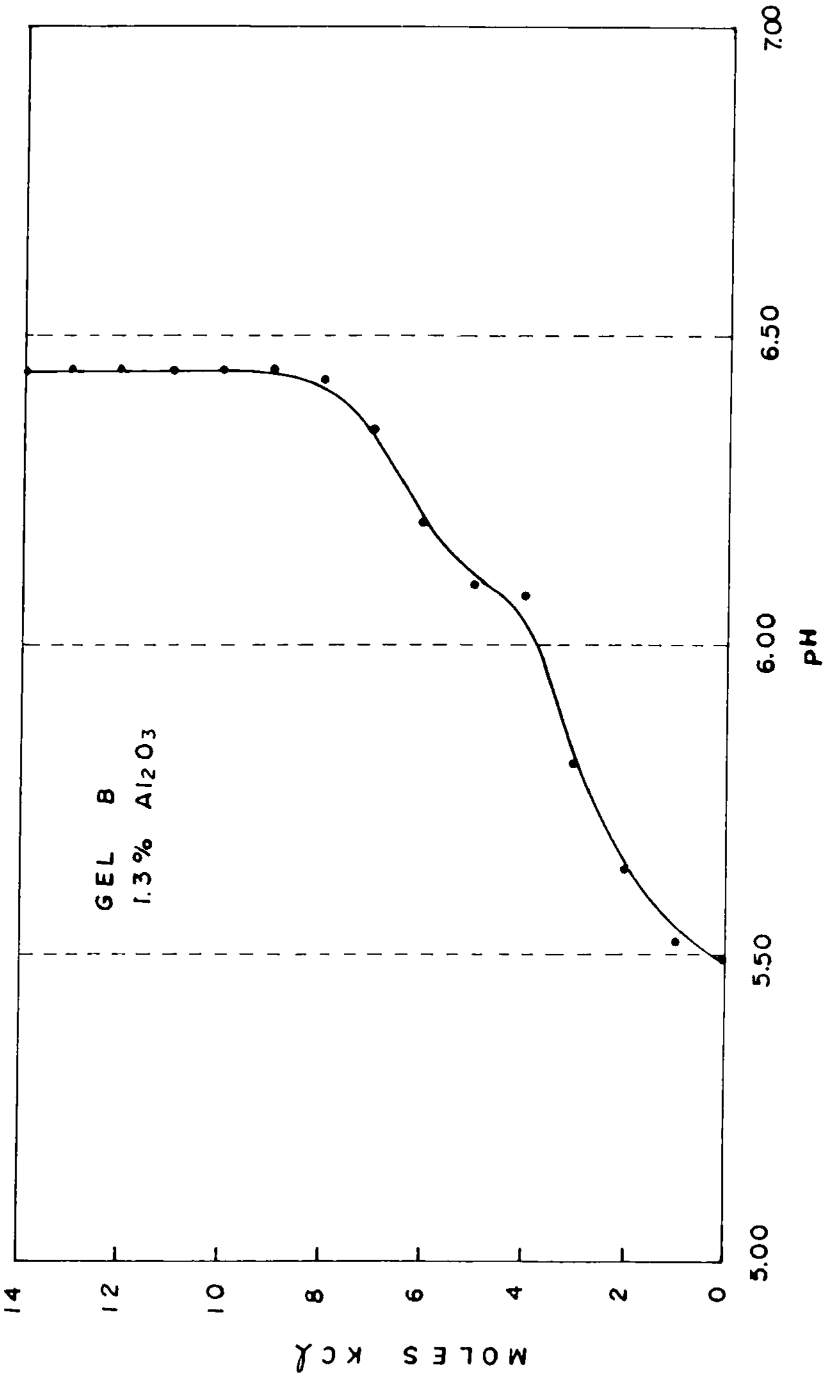

FIGURE 2

PZC determination by addition of 4M KCl

TABLE 3

SODIUM CONTENT IN ALUMINUM HYDROXYCARBONATE GELS.

SAMPLE	ACID CONSUMING CAPACITY mEq/g	SODIUM CONTENT g/L	SODIUM CONTRIBUTION mg/day
A	1.06	0.0406	10.3
B	0.81	0.0488	16.2
C	0.51	0.0507	27.0
D	0.33	0.5620	458.5

useful for the formulator in selecting the best AHC gel for his preparation, either for colloidal or pharmaceutical stability. For the raw material manufacturer, the knowledge of rate of settling is useful to optimize washing of the gels, since it will determine the time interval between successive washes, although this operation seems to be less frquently used in AHC gel manufacturing in favor of filtration following precipitation and ageing of the gel.

Figure 2 is a typical graph in PZC determination. The results of pH, PZC and surface charge are shown in Table 2.

It can be seen that all samples are within pH specifications for AHC gels (14). The PZC's of the AHC gels are within a closer range than pH values, since PZC's varied from 6.45 to 7.33 pH units, whereas pH was between 5.61 and 7.60. Surface charge ranged from - 0.38 to + 0.84. These differences indicate variations in precipitation conditions from one manufacturer to another (18) and could be considered by the formulator to select the raw material.

The relevance of surface charge is also related with the washing of the gels after precipitation. On the one hand, the rate of settling is influenced by the electrostatic interactions among particles of AHC: if the net forces due to surface charge and van der Waals forces are attractive, the particles will form agglomerates that will settle faster than individual

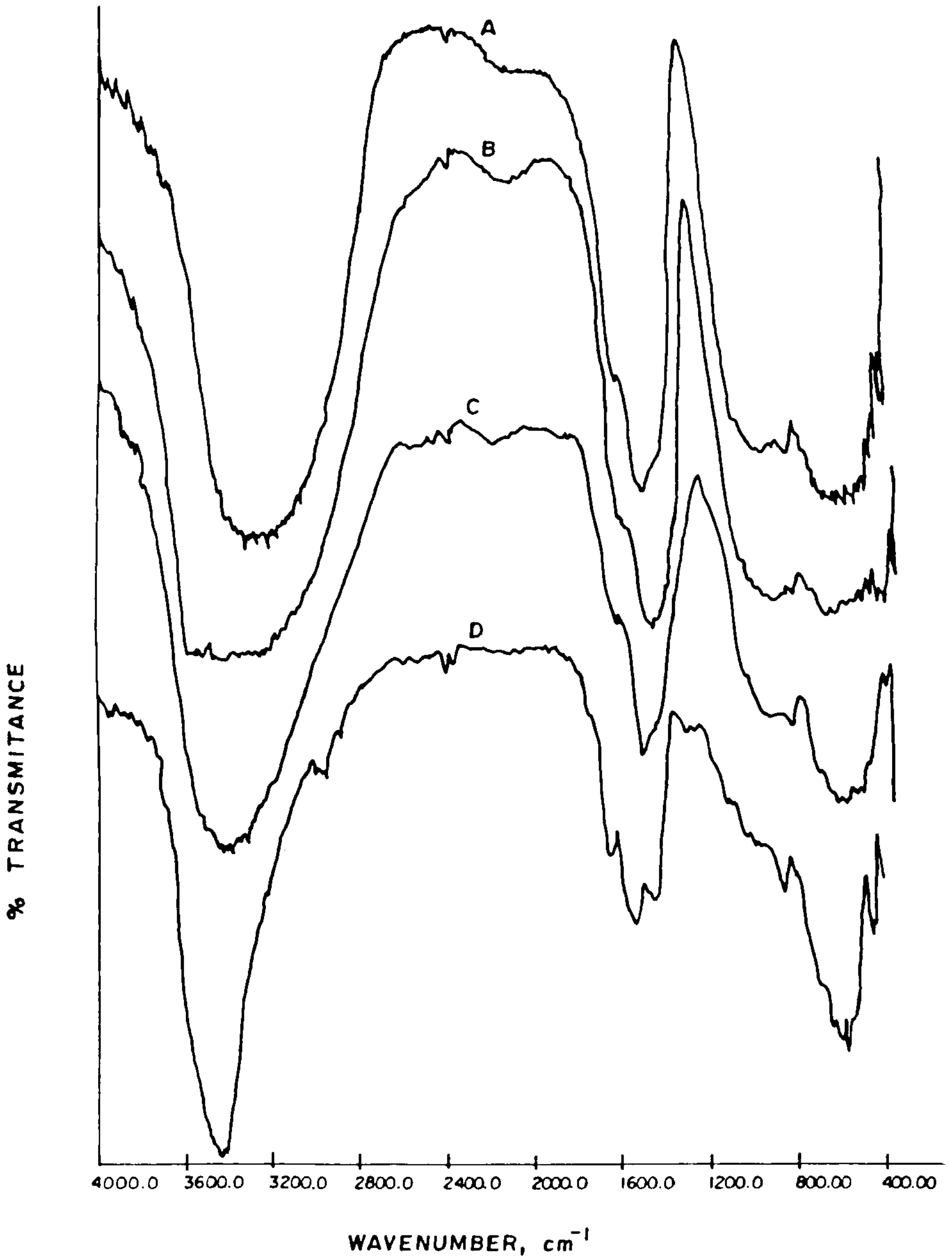

FIGURE 3

IR spectra of the four AHC gels studied.

TABLE 4

SUMMARY OF TYPICAL IR ABSORPTION BANDS OF AHC GELS AND SYNTHETIC DAWSONITE

PRODUCT	WAVE NUMBER cm^{-1}		
	STRUCTUAL HYDROXYL	MOLECULAR WATER DEFORMATION BAND	STRUCTURAL CARBONATES
AHC	3400-3600 (2)	1636	1525 and 1450; 1100, 850 (5)
A	3473	1645	1518 and 1440; 1104, 843
B	3480	1630	1518 and 1440; 1088, 850
C	3480	1638	1518 and 1440; 1096, 857
D	3444	1623	1525 and 1440; 1103, 850
Dawsonite	3290	----	1565 and 1400; 1095, 840

particles, accelerating the washing process. On the other hand, net surface charge, positive or negative, will determine the ease to eliminate cations and anions (18).

The results of sodium content in the four samples studied are reported in Table 3, where it can be observed that sample D has a sodium content of 0.562 g/L, followed by samples C, B, and A, which was the gel with the lowest sodium content of the four samples studied. As can be seen, gel D is not adequate for antacid formulations with low sodium content, since it does not comply with the requirement of 50 mg/day recommended by Hem et. al (3).

Regarding gels A, B, and C, it can be observed that sodium content is about the same although the acid consuming capacities are very different. These results impact directly in the daily sodium contribution with gel A as the most adequate to formulate antacid suspensions with low sodium content.

Figure 3 shows the IR spectrum of each of the four AHC specimens tested where can be observed the different intensity of the absorption bands for each sample. Table 4 summarizes the most important absorption bands reported in the literature for AHC gels (2), the bands obtained for the samples tested and the bands reported for synthetic dawsonite (7). Dawsonite is a natural, crystalline form of sodium aluminum hydroxycarbonate. Amorphous aluminum hydroxycarbonate is not found in natural form.

The differences observed in the IR spectra of the samples in Fig. 3 and in the data in Table 4 can be assigned to precipitation conditions used to prepare the gels, particularly pH. Scholtz et al. (2), report the IR spectra of AHC precipitated under different conditions of pH where it can be observed the effect of these changes on the intensity and position of the characteristic absorption bands of these gels. In addition, the pH of precipitation is also shown to affect the degree in which carbonates are adsorbed by the molecule of AHC, as adsorbed carbonates increase the IR spectra are more similar to that of dawsonite, whereas if the degree of carbonation decreases, the IR spectra resemble that of gibbsite, Fig. 4. It has also been reported (5) that, for sodium carbonate, the carbonate absorption band at 1450^{-1} splits in two for dawsonite and for AHC in the ranges observed in Table 4; the magnitude of the split could indicate different reactivities of the AHC, although this possibility has not been studied in detail.

The results of the infrared spectra could be useful as an identity test for AHC gels either wet or dry products to confirm results of other tests and to avoid the use of less reactive forms of aluminum hydroxide such as gibbsite, in the formulation of antacids.

CONCLUSIONS

Physicochemical characterization of AHC allows the gel manufacturer to establish the parameters to be controlled during gel precipitation in order to obtain adequate viscosity, pH and particle size distribution that facilitate processing (washing, filtration) and also to prepare raw materials with low settling rates and low sodium content.

The settling rates of the four suspensions of AHC gels agree, in general, with the predictions of Stokes

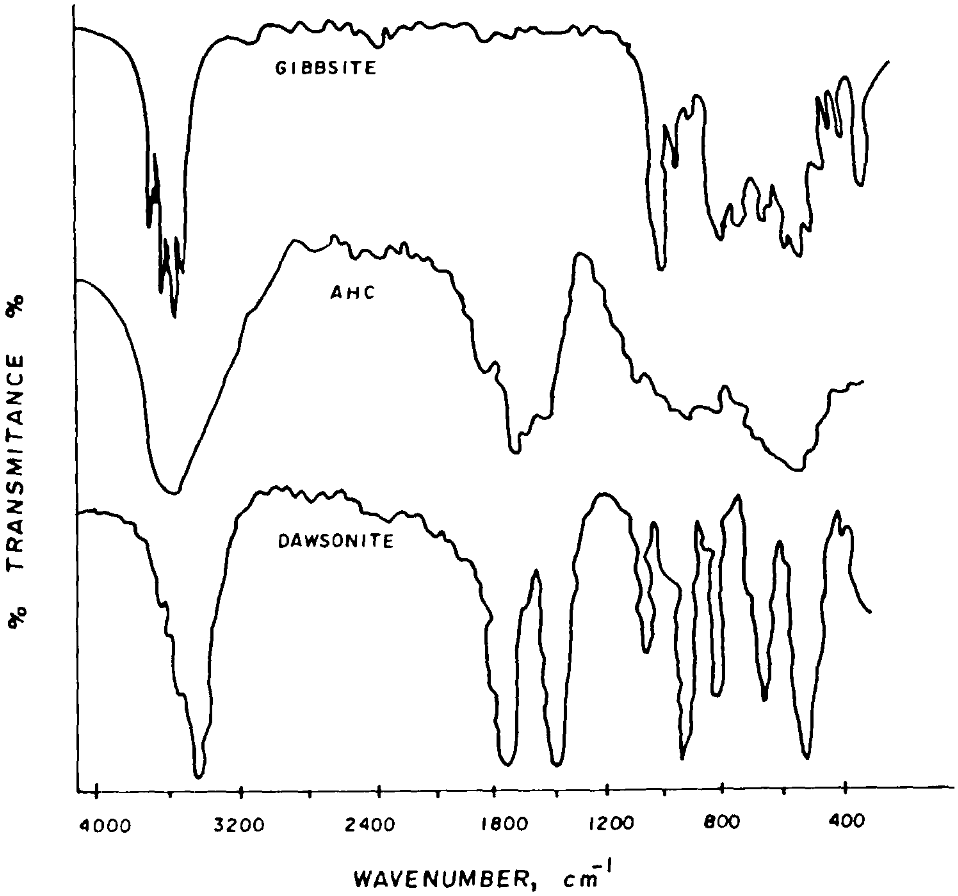

FIGURE 4

Comparison of IR spectra of gibbsite, AHC precipitated at pH = 7.0 and dawsonite (Adapted from reference 2).

law. The deviations observed can be explained as due to the existence of net surface charges that promote particle-to-particle interactions. Low settling rates of AHC gels are also desirable since they favored formulation of antacid suspensions with colloidal stability that impart desirable aesthetic properties to the preparation and ensures uniform dose-to-dose administration. The four gels meet the specifications for pH in 4% w/w equivalent $Al(OH)_3$ Further, three of the gels (A, B and C) also meet the recommendation to prepare antacid formulations with low sodium content, i. e., no more than 50 mg/day in patients in a strict sodium-restricted diet. The PZC and the IR spectra indicate precipitation conditions that vary from one manufacturer to another. The intensity and position of the absorption bands of the amorphous AHC samples indicate different degrees of carbonation obtained during precipitation of the gels. It would be interesting to study the possible relation between the magnitude of the partition band of the carbonate in AHC with the gel reactivity. The commercial gels of AHC studied in this work were identified by IR spectroscopy as amorphous AHC. This fact is useful to differentiate reactive $Al(OH)_3$ from non-reactive forms, such as gibbsite, and could lead to a pharmacopeial IR identity test.

REFERENCES

1. E.C. Scholtz, J.R. Feldkamp, J.L. White and S.L. Hem, J. Pharm. Sci., 73, 1007 (1984).
2. E.C. Scholtz, J.R. Feldkamp, J.L. White and S.L. Hem, J. Pharm. Sci., 73, 967 (1984).
3. S.L. Hem, J.L. White, J.D. Buehler, J.R. Luber, W.M. Grim and E.A. Lipka, Am. J. Hosp. Pharm., 3,1925 (1982).
4. P.R. Nixon, J.L. White and S.L. Hem, J. Colloid Interface Sci., 120, 312 (1987).
5. J.L. White and S.L. Hem, J. Pharm. Sci., 64, 468 (1975).
6. J.L. White, S.L. Nail and S.L. Hem, Seventh Conference on Clay Mineralogy and Petrology, Karlovy Vary (1976).
7. C.J. Serna, J.L. White and S.L. Hem, Clays and Clay Minerals, 25, 384 (1977).
8. C.J. Serna, J.L. White and S.L. Hem, Soil Sci. Soc. Am. J., 41, 1009 (1977).
9. C.J. Serna, J.L. White and S.L. Hem, J. Pharm. Sci., 67, 324 (1978).
10. C.J. Serna, J.L. White and S.L. Hem, J. Pharm. Sci., 67, 1144 (1978).
11. R.B. Bird, W. E. Stewart and E. N. Lightfoot, "Transport Phenomena", Wiley, New York (1960).
12. J.S. Tempio and J. L. Zatz, J. Pharm. Sci., 69, 1209 (1980).

13. M.A. Hughes, in "Solid-Liquid Separation," L. Svarovsky, editor, Third Edition, Butterworth-Heinemann, Oxford (1990).
14. The United States Pharmacopeia. The National Formulary. United States Pharmacopeial Convention, Inc. Rockville, MD, XXII, 1990.
15. J.C. Liu, J.R. Feldkamp, J.L. Hem, N. Otsuba, D.F. Conroy, C.M. Pendharkar, K.M. Feld, R.J. Harwood and W.M. Grim, Drug. Dev. Ind. Pharm., 13, 2087 (1987).
16. CINVESTAV. Reporte No. 5 a Química y Farmacia, S. A. de C. V. Centro de Investigación y Estudios Avanzados, IPN, Unidad Saltillo, México (1992).
17. S.L. Hem, "Theory of Suspensions". Unpublished notes (1990).
18. E.C. Scholtz, J.R. Feldkamp, J.L. White and S.L. Hem, J. Pharm. Sci., 74, 478 (1985).