RESEARCH ARTICLES

Mechanism of Freeze–Thaw Instability of Aluminum Hydroxycarbonate and Magnesium Hydroxide Gels

MARY I. ZAPATA *, JOSEPH R. FELDKAMP ‡, GARNET E. PECK *, JOE L. WHITE ‡, and STANLEY L. HEM *ˣ

Abstract ☐ The effect of freeze–thaw cycles on the physical stability of aluminum hydroxycarbonate and magnesium hydroxide gels was studied. Coagulation following a freeze–thaw cycle, leading to the formation of visible aggregates, affected the content uniformity of both gels. The freeze–thaw cycles did not affect the crystal form or surface characteristics of the gels as determined by X-ray powder diffraction and point of zero charge, but caused a slight reduction in the rate of acid neutralization and a large increase in the rate of sedimentation. The greatest effect was observed after the first freeze–thaw cycle. While the duration of freezing was not a factor, the rate of freezing was important and was inversely related to the aggregate size. The aggregates which formed following a freeze–thaw cycle were not redispersed by shaking, but were reversed by ultrasonic treatment or homogenization. The adsorption of polymers or surface-active agents prior to freezing reduced and, in some cases, prevented the formation of aggregates. The physical instability produced by a freeze–thaw cycle was explained by the modified DLVO theory. The force exerted on the particles by the growing ice crystals forced the particles into the primary minimum, producing strong interparticle attraction. On thawing, simple agitation did not provide enough force to overcome the attractive force of the primary minimum. Adsorption of polymers or surface-active agents increased the steric repulsive force and prevented the particles from reaching the primary minimum.

Keyphrases ☐ Aluminum hydroxycarbonate gel—freeze–thaw instability, mechanism, effect of added polymers and surface-active agents ☐ Magnesium hydroxide gel—freeze–thaw instability, mechanism, effect of added polymers and surface-active agents ☐ Freeze–thaw cycles—stability of aluminum hydroxycarbonate and magnesium hydroxide gels, effects of added polymers and surface-active agents, mechanisms

A pharmaceutical suspension must be composed of small, uniformly sized particles which do not settle rapidly and which can be easily redispersed to provide the patient with an accurate dose. Unfortunately, the physical characteristics of many suspensions are adversely affected by freeze–thaw cycles, causing the formation of visible lumps which settle rapidly and do not redisperse even after vigorous shaking (1). Aluminum hydroxycarbonate and magnesium hydroxide gels are widely recognized examples of suspensions whose physical stability is adversely affected by freeze–thaw cycles. Products containing these gels frequently bear a warning on the label to protect from freezing.

The homogeneity of parenteral chloramphenical suspensions is affected so adversely by freeze–thaw cycles that they can not be administered due to needle blockage (2). The rate of sedimentation of insulin suspensions was at least three times faster after undergoing a freeze–thaw cycle (3). The rate of thawing of the frozen insulin suspensions did not affect the sedimentation rate. The biological activity of the insulin suspensions was not affected by the freeze–thaw cycle, but it was difficult to obtain a reproducible dose. A change in particle size distribution following a freeze–thaw cycle has also been observed for suspensions of titanium dioxide, zinc oxide, glass beads, prednisolone acetate, and sulfadimethoxine (2).

Physical stability problems, such as oil separation, have been associated with freeze–thaw cycles of oil-in-water emulsions (1, 4–8). The mechanism responsible for the freeze–thaw instability of emulsions is not fully understood, but a common mechanism may be operating in both suspensions and emulsions.

The present study was undertaken to investigate the mechanism responsible for the freeze–thaw instability of suspensions in the belief that this basic information will lead to methods of stabilizing suspensions which are exposed to freezing. Gels of aluminum hydroxycarbonate and magnesium hydroxide were chosen as model suspensions because of their history of freeze–thaw stability problems. In addition, these gels provide a valuable comparison as

Table I—Percent of Theoretical Dose Obtained Under Simulated Administration of Aluminum Hydroxycarbonate and Magnesium Hydroxide Gels

Aluminum Hydroxycarbonate Gel		Magnesium Hydroxide Gel	
Never Frozen	After One Freeze–Thaw Cycle	Never Frozen	After One Freeze–Thaw Cycle
99.6	118.2	99.1	136.9
99.6	109.8	99.1	121.8
99.6	112.0	99.1	109.3
99.6	108.4	99.1	83.6
99.1	110.9	99.1	100.0
99.6	113.8	98.7	132.4
98.7	117.8	99.1	101.3
99.6	112.0	99.1	92.4
99.6	107.8	99.1	91.6
99.6	109.3	99.1	92.4
Mean 99.5	112.0	99.1	106.2
SD 0.3	3.6	0.1	18.4

aluminum hydroxycarbonate gel is amorphous, but can undergo transformation to crystalline polymorphs, while magnesium hydroxide gel possesses the stable crystalline structure of the mineral brucite (9).

EXPERIMENTAL

The aluminum hydroxycarbonate and magnesium hydroxide gels studied were prepared by diluting a commercial aluminum hydroxycarbonate gel to 4% equivalent aluminum oxide or a commercial magnesium hydroxide gel to 6.8% magnesium hydroxide with doubly distilled water and homogenizing[1]. A standard procedure was followed for the freeze–thaw cycle. The gel (350 mL) in a 500-mL linear polyethylene bottle was placed in a freezer at −24°C. After 24 h, the sample was returned to room temperature. The effect of a rapid freezing rate was determined by immersing a 350-mL sample contained in a 500-mL linear polyethylene bottle in an acetone–dry ice bath (−86°C) for 24 h.

The aluminum or magnesium content was determined by chelatometric titration (10) and was expressed as equivalent aluminum oxide or magnesium oxide. The content uniformity was determined by inverting the 350-mL sample 20 times and immediately withdrawing a sample which would theoretically neutralize 3.75×10^{-4} M equivalent Al_2O_3. The sample was withdrawn by syringe and accurately weighed. The moles of acid actually neutralized by the sample at pH 3.0, 25°C was determined by an automated[2] pH-stat titration (11).

Samples were prepared for X-ray diffraction by air drying the gel and preparing a power by trituration with an agate mortar and pestle. Randomly oriented powder samples were prepared in McCreery mounts. Diffractograms were recorded[3] from 4° to 65° 2θ under the following conditions: CuK_α radiation, 30 kV, 28 mA, 1000 cps, and 2°/min.

A titration technique (12, 13) was used to determine the point of zero charge. The rate of acid neutralization was determined by an automated pH-stat titration at pH 3.0, 25°C and expressed as t_{50}, the time required for 50% of the theoretical amount of acid to be neutralized (11). The rate of sedimentation was determined by monitoring the density[4] of the upper region of the sample (14). Entrapped air was removed from the sample by placing 350 mL in a 1-L sidearm flask and applying vacuum for 15 min.

Samples were examined microscopically at a magnification of 400× using the following dilutions: aluminum hydroxycarbonate gel, 1 drop of gel with 4 drops of supernatant; aluminum hydroxycarbonate gel after one freeze–thaw cycle, 1 drop of gel with 2 drops of supernatant; magnesium hydroxide gel, 1 drop of gel with 6 drops of supernatant; and magnesium hydroxide gel after one freeze–thaw cycle, no dilution.

Samples were processed using the following equipment: ultrasonic dispersor[5] for 12 min at an output control of 4, one pass through a colloid mill[6] at a clearance of 7.62×10^{-3} cm, one pass through a hand homoge-

Table II—X-ray Diffractogram of Magnesium Hydroxide Gel Before and After Freeze–Thaw Cycles

	dhkl (I/I_0)		
	Magnesium Hydroxide Gel		
Brucite[a]	Never Frozen	After 1 Freeze–Thaw Cycle	After 10 Freeze–Thaw Cycles
4.77(90)	4.7663(40)	4.7663(41)	4.7663(38)
2.72(6)	2.7281(4)	2.7281(4)	2.7281(5)
2.365(100)	2.3659(100)	2.3659(100)	2.3659(100)
1.7941(55)	1.7957(38)	1.7957(38)	1.7957(38)
1.573(35)	1.5739(35)	1.5739(35)	1.5739(34)
1.494(19)	1.4955(14)	1.4955(14)	1.4955(14)

[a] *Selected Powder Diffraction Data for Minerals*, Joint Committee on Powder Diffraction Standards, Swathmore, Pa. 1947, File 7-239.

nizer set at the smallest opening, and a magnetic stirrer for 12 min. Samples containing hydroxypropyl methylcellulose[7], sodium lauryl sulfate, cetyltrimethylammonium bromide, or polysorbate 80 were prepared by appropriate dilution of stock solutions.

The surface tension of the supernatant of surface-active agent–aluminum hydroxycarbonate gel mixtures was measured with a DuNouy tensiometer[8]. The average of three readings was reported. The following procedure was necessary to obtain a clear supernatant:

1. The equilibrated surface-active agent–aluminum hydroxycarbonate gel mixture was centrifuged at 6000 rpm for 20 min and the supernatant (cloudy) was collected.

2. The pH of the supernatant was adjusted to the point of zero charge of the aluminum hydroxycarbonate gel (pH 6.7) with 0.5 M NaOH (the number of drops was recorded).

3. The mixture was centrifuged at 5000 rpm for 10 min, and the supernatant (clear) was collected. The surface tension of solutions containing the same concentration of surface-active agent and 0.5 M NaOH served as controls.

RESULTS AND DISCUSSION

Aluminum hydroxycarbonate and magnesium hydroxide gels exhibit excellent content uniformity, as the mean dose was within 99% of the theoretical following the simulated administration of 10 doses (Table I). However, the ability to obtain an accurate dose of either gel was lost following one freeze–thaw cycle. Lumps were observed in both gels following the freeze–thaw cycle; however, the lumps in the magnesium hydroxide gel appeared to be larger. This difference may be responsible for the greater standard deviation for magnesium hydroxide (±18.4%) than for aluminum hydroxycarbonate gel (±3.6%) following a freeze–thaw cycle.

Freeze–thaw cycles did not affect the polymorphic form of the solid phase, as aluminum hydroxycarbonate gel remained amorphous by X-ray diffraction after 10 freeze–thaw cycles. The X-ray diffractogram of magnesium hydroxide gel was identical to brucite and did not change after 10 freeze–thaw cycles (Table II). Freeze–thaw cycles also do not
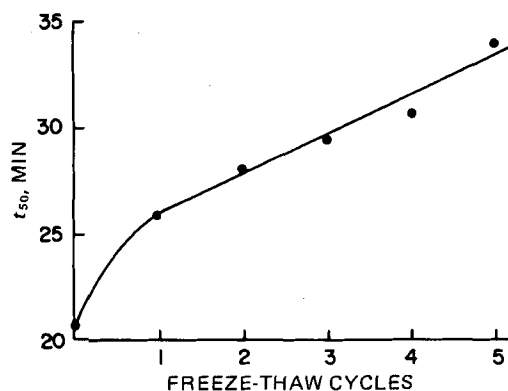

Figure 1—*Effect of repeated freeze–thaw cycles on the rate of acid neutralization of aluminum hydroxycarbonate gel.* t_{50} *represents the time required for 50% of the theoretical amount of acid to be neutralized at pH 3.*
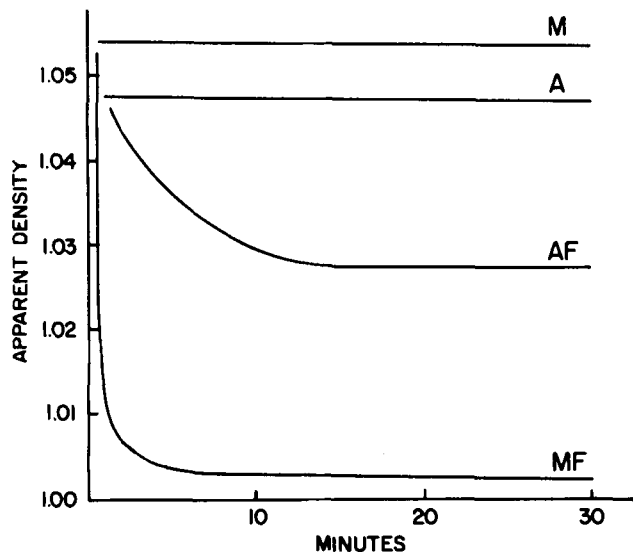
Figure 2—*Apparent density of the upper region of aluminum hydroxycarbonate or magnesium hydroxide gels. Key: (M) magnesium hydroxide gel, never frozen; (MF) magnesium hydroxide gel after one freeze–thaw cycle; (A) aluminum hydroxycarbonate gel, never frozen; (AF) aluminum hydroxycarbonate gel after one freeze–thaw cycle.*

appear to affect the surface groups of either gel as the point of zero charge (ZPC) was unaltered by 10 freeze–thaw cycles (ZPC of aluminum hydroxycarbonate, 6.7; ZPC of magnesium hydroxide, 10.8).

The rate of acid neutralization decreased slightly following freeze–thaw cycles. This effect was seen most clearly for aluminum hydroxycarbonate gel (Fig. 1). The initial freeze–thaw cycle caused the greatest decrease in the rate of acid neutralization, although a consistent decrease in the rate of acid neutralization occurred following each freeze–thaw cycle. The rate of acid neutralization of magnesium hydroxide is so rapid (t_{50}, 1.3 min) that the small effect of a freeze–thaw cycle was difficult to detect.

The decrease in the rate of acid neutralization was too small to attribute to the formation of a crystalline phase in aluminum hydroxycarbonate gel, as the crystalline forms of aluminum hydroxide are virtually unreactive at pH 3 (10). Thus both the X-ray diffraction and rate of acid neutralization data conflict with Gamame and Yoshida's (15) conclusion that freeze–thaw cycles promote the crystallization of aluminum hydroxide. An explanation for this apparent discrepancy is that Gamame and Yoshida used chloride-, nitrate-, and sulfate-containing aluminum hydroxide gels, which convert to crystalline forms very rapidly under normal aging (16, 17).

The duration of freezing is not significant, as samples of aluminum hydroxycarbonate or magnesium hydroxide gel which were frozen for 1, 3, 5, or 7 d all exhibited the same rate of acid neutralization (t_{50}, 26.0 min.). The freeze–thaw process seems to be the key element rather than the duration of freezing.

The rate of sedimentation as measured by the decrease in the density of the upper region of the sample proved to be a good indicator of the effects of a freeze–thaw cycle on the particle size distribution (14). The density of the upper region of aluminum hydroxycarbonate or magnesium hydroxide gel which had never been frozen remained essentially constant for at least 30 min, indicating a very low rate of sedimentation (Fig. 2). However, the density of the upper region of each gel decreased sharply following a freeze–thaw cycle. The sedimentation method is not as sensitive to the effect of repeated freeze–thaw cycles as the rate of acid neutralization, because a similar density curve was obtained regardless of the number of freeze–thaw cycles while the rate of acid neutralization steadily decreased with repeated freeze–thaw cycles (Fig. 1).

The greater particle size of magnesium hydroxide gel following a freeze–thaw cycle, which was suggested by the content uniformity data in Table I, was confirmed by the density data in Fig. 2. The density of the upper region of the aluminum hydroxycarbonate gel dropped rapidly to 1.0275 following a freeze–thaw cycle while the density of the upper region of the magnesium hydroxide gel rapidly approached the density of water. This indicates that the rate of sedimentation in magnesium hydroxide gel following a freeze–thaw cycle was very rapid and produced a particle-free upper region within several minutes. Photomicrographs of aluminum hydroxycarbonate and magnesium hydroxide gels confirm that
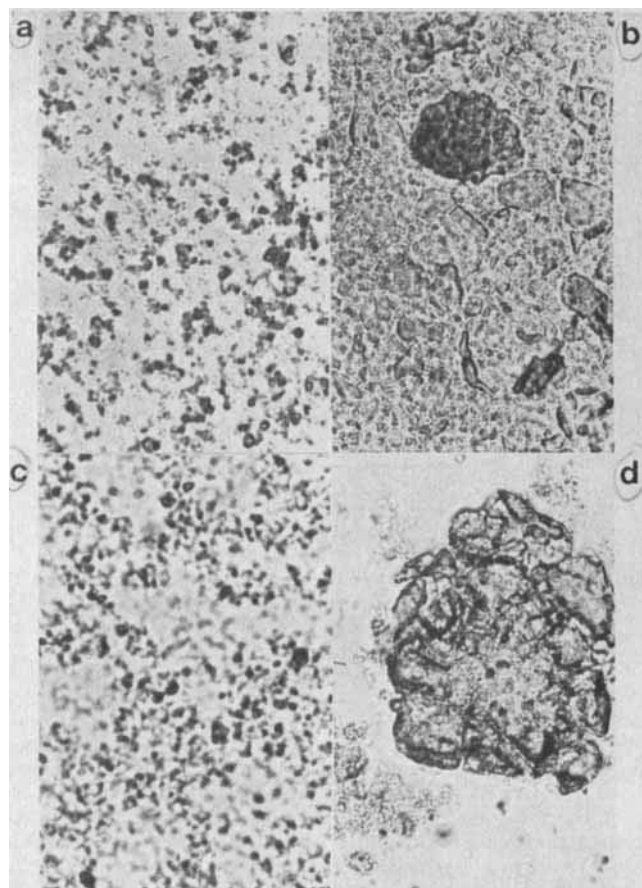

Figure 3—*Photomicrographs of gels at an original magnification of 400X. Key: (a) aluminum hydroxycarbonate gel; (b) aluminum hydroxycarbonate gel after one freeze–thaw cycle; (c) magnesium hydroxide gel; (d) magnesium hydroxide gel after one freeze–thaw cycle.*

aggregates ranging from ~65 to 160 μm form following a freeze–thaw cycle (Fig. 3).

The effects of a freeze–thaw cycle were reversed if adequate energy was applied to the suspension. As observed in Fig. 4, magnesium hydroxide gel which had undergone a freeze–thaw cycle was restored to its original settling characteristics by treatment with an ultrasonic dispersor. The effectiveness of various processing methods in restoring the original particle size distribution of the magnesium hydroxide gel appears (Fig. 4) to be directly related to the energy input as the order of effectiveness was ultrasonic dispersor > hand homogenizer > colloid mill > magnetic stirrer. The settling characteristics of aluminum hydroxycarbonate gel were similarily restored by the processing equipment.

The rate of freezing was found to be an important factor in the formation of aggregates during a freeze–thaw cycle. The rate of sedimentation of aluminum hydroxycarbonate gel was unaffected (identical to curve A in Fig. 2) if the gel was exposed to an acetone–dry ice bath (−86°C) to produce a rapid rate of freezing, while a slower rate of freezing (freezer at −24°C) resulted in an increased particle size (identical to curve AF in Fig. 2).

The importance of the freezing process and the rate of freezing, the absence of crystallization following freeze–thaw cycles, and the ability of high shear to reverse the effects of the freeze–thaw cycle all led to the

Table III—Effect of Hydroxypropyl Methylcellulose on Rate of Acid Neutralization of Aluminum Hydroxycarbonate Gel at pH 3.0

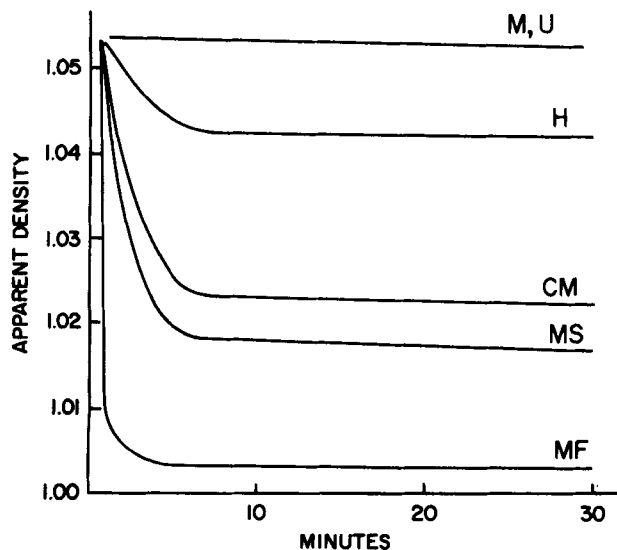| Hydroxypropyl Methylcellulose, %	t_{50}, min
0	38
1	39.5
3	40.5
5	42
7	44.5

Figure 4—*Apparent density of the upper region of magnesium hydroxide gel. Key: (M) never frozen; (MF) after one freeze–thaw cycle; (U) ultrasonic dispersor after one freeze–thaw cycle; (H) hand homogenizer after one freeze–thaw cycle; (CM) colloid mill after one freeze–thaw cycle; (MS) magnetic stirrer after one freeze–thaw cycle.*

hypothesis that the freezing process forces the particles to form aggregates as described by the modified DLVO theory (Fig. 5) (18–22). The strong force exerted on the particles by ice formation was sufficient to overcome the repulsive barrier known as the primary maximum, and the particles were forced close enough together to experience the strong attractive force present in the primary minimum, thus forming aggregates. When the ice thawed, the aggregates remained intact unless enough energy was applied to overcome the energy barrier imposed by the primary maximum. The appearance of aggregates, the increased rate of sedimentation, the slight decrease in rate of acid neutralization, and the reversibility under high shear are all consistent with this mechanism.

The effect of the rate of freezing was also consistent with the modified DLVO theory. The more rapid rate of freezing caused a greater rate of nucleation and, therefore, a lower rate of crystal growth (23). The smaller ice crystals which were formed during the more rapid rate of freezing did not force as many suspension particles into an aggregate as occurred when large ice crystals formed during a slow rate of freezing. Therefore, aggregate size is inversely related to the rate of freezing. Furthermore, both theoretical and experimental studies showed that the maximum force exerted on a fixed spherical particle by a freezing interface was inversely related to the freezing rate (24, 25). Thus, the suspension particles experience a smaller force during a rapid freezing process.

The modified DLVO theory includes steric repulsive forces which are dependent on the size, geometry, and conformation of adsorbed molecules. Lecithin monolayers have been reported to exhibit strong repulsion at separation distances <20 Å (26). Steric repulsive forces have been observed on the close approach of mica sheets in an aqueous medium containing polyethylene oxide (27). A sharp increase in the repulsive force, which was attributed to forcing the polymer from between the mica surfaces, was observed when the distance of separation of the mica sheets was <5 Å.

It was hypothesized that adsorption of appropriate solutes will minimize aggregate formation during a freeze–thaw cycle by enhancing the primary maximum through the introduction of steric repulsive forces.

Table IV—Difference in Density of the Upper Region of Aluminum Hydroxycarbonate Gel Containing Various Concentrations of Hydroxypropyl Methylcellulose Following a Freeze-Thaw Cycle

Hydroxypropyl Methylcellulose, %	Initial Density	Equilibrium Density[a]	Δ Density
0	1.050	1.027 (10 min)	0.023
1	1.055	1.035 (10 min)	0.020
3	1.060	1.040 (10 min)	0.020
5	1.070	1.055 (15 min)	0.015
7	1.075	1.065 (20 min)	0.010

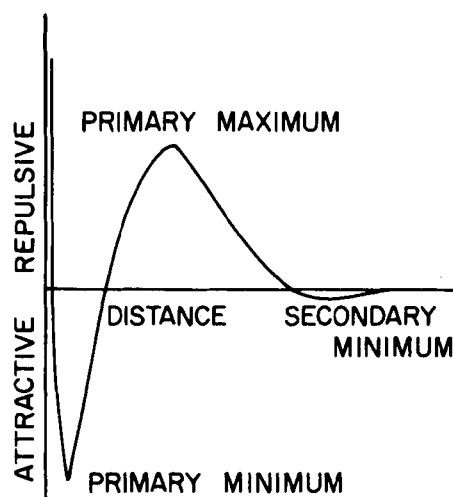[a] Time to reach equilibrium density in parentheses.

Figure 5—*Interparticle forces described by the modified DLVO theory.*

This hypothesis was tested by determining the effect of a polymer and several surface-active agents on the freeze–thaw stability.

Hydroxypropyl methylcellulose was adsorbed by aluminum hydroxycarbonate gel as evidenced by the decreased rate of acid neutralization in the presence of increased quantities of hydroxypropyl methylcellulose (Table III). The adsorbed hydroxypropyl methylcellulose was believed to reduce the rate of acid neutralization by occluding the surface and interfering with the approach of protons (28). The reduced rate of acid neutralization was not believed to be due to changes in viscosity as the hydroxypropyl methylcellulose–aluminum hydroxycarbonate gel sample was diluted 20 times prior to the pH-stat titration.

The addition of hydroxypropyl methylcellulose increased both the density and viscosity of the aluminum hydroxycarbonate gel. Therefore, to monitor the effect of a freeze–thaw cycle on the particle size distribution of the hydroxypropyl methylcellulose-containing aluminum hydroxycarbonate gel, it was necessary to modify the sedimentation procedure by comparing the difference in apparent density between the initial value (which increased with increasing hydroxypropyl methylcellulose concentration) and the relatively constant density which was ultimately reached. As seen in Table IV, aggregate formation due to a freeze–thaw cycle was reduced in direct relation to the concentration of hydroxypropyl methylcellulose.

The ability of polymers to minimize the effects of a freeze–thaw cycle was previously observed for polyvinylpyrrolidone, polyvinyl alcohol, methylcellulose, sodium carboxymethylcellulose, pectin, tragacanth, and sodium alginate (29). The protective effect was attributed to the formation by the polymer of a three-dimensional network in the aqueous phase which reduced the growth of ice crystals and immobilized the suspended particles, thereby reducing the formation of aggregates. While the structuring effect of polymers on the aqueous phase may be important and may have occurred in the hydroxypropyl methylcellulose–aluminum hydroxycarbonate system, it does not explain the protective effect which was also observed when surface-active agents were adsorbed by aluminum hydroxycarbonate or magnesium hydroxide gel.

The effect of sodium lauryl sulfate (an anionic surface-active agent), cetyltrimethylammonium bromide (a cationic surface-active agent), and polysorbate 80 (a neutral surface-active agent) on the freeze–thaw stabilities of aluminum hydroxycarbonate and magnesium hydroxide gels was studied. The rate of acid neutralization was reduced by the presence of the surface-active agents, with sodium lauryl sulfate causing the greatest effect (Table V). The reduction in the rate of acid neutralization was believed to be due to adsorption of the surface-active agents. Greater adsorption of sodium lauryl sulfate was expected, as both gels are positively charged under the conditions of the test (ZPC of aluminum hy-

Table V—Effect of Surface-Active Agents on the Rate of Acid Neutralization of Aluminum Hydroxycarbonate Gel at pH 3.0

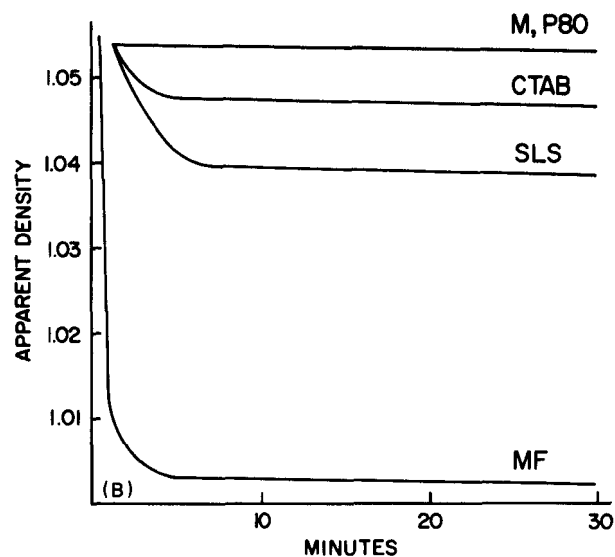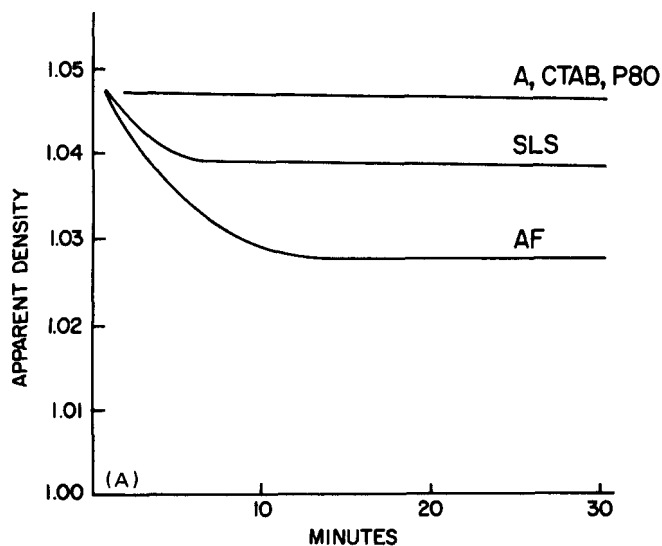| Adsorbate	t_{50}, Min
Control	20.8
2.4×10^{-2} M Sodium lauryl sulfate	27.2
2.0×10^{-2} M Cetyltrimethylammonium bromide	22.2
2.6×10^{-2} M Polysorbate 80	22.5

Figure 6—*Apparent density of the upper region of (A) aluminum hydroxycarbonate and (B) magnesium hydroxide gels. Key: (A, M) never frozen; (AF, MF) after one freeze–thaw cycle; (CTAB) containing 2.0 × 10⁻² M cetyltrimethylammonium bromide after one freeze–thaw cycle; (SLS) containing 2.4 × 10⁻² M sodium lauryl sulfate after one freeze–thaw cycle; (P80) containing 2.6 × 10⁻² M polysorbate 80 after one freeze–thaw cycle.*

droxycarbonate gel 7.6, pH 5.4; ZPC of magnesium hydroxide gel 10.8, pH 9.9). Therefore, the greater reduction in the rate of acid neutralization which occurred when sodium lauryl sulfate was present confirms the adsorption hypothesis.

Adsorption of the surface-active agents was confirmed by a comparison of the surface tension of a solution of the surface-active agent with the surface tension of the supernatant after equilibration of the gel with the same solution of surface-active agent (Table VI) (30). Sodium lauryl sulfate was the most readily adsorbed agent, as the surface tension of the supernatant was 10–15 dynes/cm higher than the surface tension of the control solution. Adsorption of cetyltrimethylammonium bromide and polysorbate 80 also occurred, as the surface tension of each supernatant was greater than the control solution. In addition, it is likely that the freezing process favors adsorption since the solute will be concentrated in a solution of unfrozen water at the solid–liquid interface as freezing proceeds.

Each of the surface-active agents reduced aggregate formation following a freeze–thaw cycle (Fig. 6). Polysorbate 80 was the most effective surface-active agent in preventing an increase in the particle size distribution of either gel, while sodium lauryl sulfate was the least effective. The relative effectiveness of the surface-active agents can be rationalized based on the adsorption mechanism and the dimensions of the surface-active agent. The expected orientation of the adsorbed agents is shown in Fig. 7. The negative hydrophilic region of sodium lauryl sulfate will be adsorbed by the positive surface. However, the hydrophobic region will also be adsorbed (31), thereby reducing the thickness of the adsorbed layer. The hydrophobic region of cetyltrimethylammonium bromide will be adsorbed, while the positive hydrophilic region will experience electrostatic repulsion with the positive surface. The hydrophobic region of polysorbate 80 will be adsorbed, while the hydrophilic region will undergo little or no adsorption due to its compatibility with water.
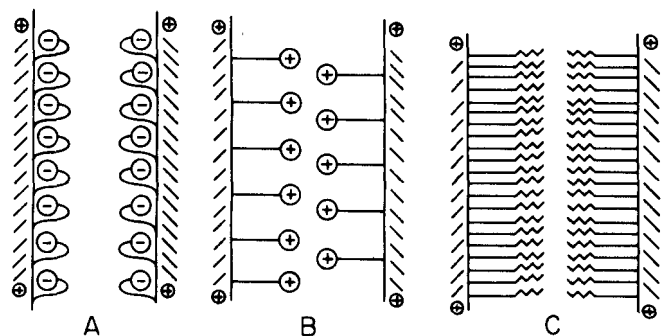

Figure 7—*Hypothetical steric repulsive region on adsorption of various surface-active agents. Key: (A) sodium lauryl sulfate; (B) cetyltrimethylammonium bromide; (C) polysorbate 80.*

The estimated molecular length of the surface-active agents is: sodium lauryl sulfate, 53 Å; cetyltrimethylammonium bromide, 76 Å; and polysorbate 80, 786 Å. Thus, the expected orientation of the adsorbed sodium lauryl sulfate suggests a steric repulsive region substantially <53 Å. The expected orientation of adsorbed cetyltrimethylammonium bromide suggests a steric repulsive region of ~76 Å. Polysorbate 80 will produce the largest steric repulsive region due to its large size and expected orientation. Examination of Fig. 6 reveals that the effectiveness of the surface-active agents in minimizing aggregate formation following a freeze–thaw cycle was directly related to the predicted size of the steric repulsive region produced by adsorption of the surface-active agent.

To determine if surface-active agents can produce disaggregation when added to a suspension following a freeze–thaw cycle, a sample of aluminum hydroxycarbonate gel was frozen for 24 h and then thawed. Polysorbate 80 was added with gentle stirring after thawing. Figure 8 shows that addition of a surface-active agent following a freeze–thaw cycle was partially effective in restoring the original particle size distribution. It has been reported (32) that irregular particles, when coagulating, will only come in contact at a limited number of points. Therefore, it is believed that polysorbate 80 added after a freeze–thaw cycle was adsorbed on the accessible interparticle space of the aggregates. The adsorption of polysorbate 80 produced a steric repulsive force between the particles, which led to partial disaggregation. However, the most effective steric repulsion
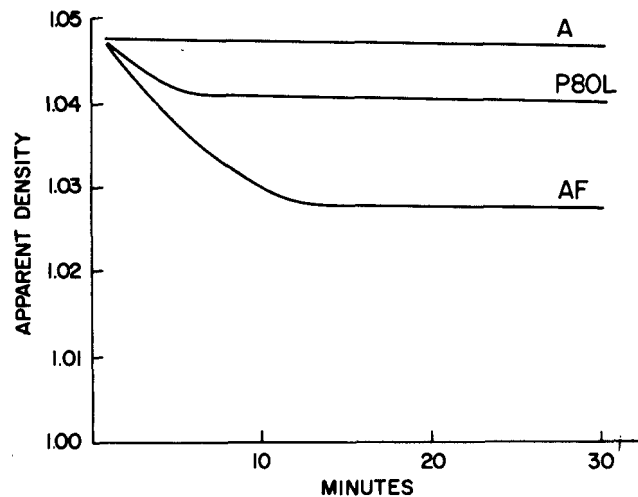

Figure 8—*Apparent density of the upper region of aluminum hydroxycarbonate gel. Key: (A) never frozen; (AF) after one freeze–thaw cycle; (P80L) 2.4 × 10⁻² M polysorbate 80 added after one freeze–thaw cycle.*

Table VI—Comparison of Surface Tension of Solutions of Surface-Active Agents to the Surface Tension of the Supernatant After Equilibration with Aluminum Hydroxycarbonate Gel

Surface-Active Agent	Concentration, M	Surface Tension of Solution, dynes/cm	Surface Tension of Supernatant, dynes/cm
Sodium lauryl sulfate	5×10^{-5}	62	72
	1×10^{-4}	57	72
	2×10^{-4}	48	70
	3×10^{-4}	44	60
	4×10^{-4}	43	59
	5×10^{-4}	42	57
Cetyltrimethylammonium bromide	5×10^{-5}	52	55
	1×10^{-4}	49	52
	2×10^{-4}	47	50
	3×10^{-4}	44	47
	4×10^{-4}	40	41
	5×10^{-4}	40	41
Polysorbate 80	5×10^{-6}	44	45
	1×10^{-5}	41	42
	5×10^{-5}	39	40
	1×10^{-4}	38	39
	2×10^{-4}	38	38
	3×10^{-4}	38	38

was produced when the surface-active agent was adsorbed before the suspension was exposed to a freeze–thaw cycle.

Although only gels of aluminum hydroxycarbonate and magnesium hydroxide were examined, it is believed that the results of this study can be applied to any suspension and that the aggregation produced by freeze–thaw cycles will be more pronounced as the particle size of the suspension is smaller.

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