Exchange of Sodium by Magnesium in Aluminum Hydroxycarbonate Gel

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Abstract □ Approximately 90% of the sodium present in a washed aluminum hydroxycarbonate gel was removed by exchange with magnesium. This behavior supports recent structural studies which have suggested that cations such as sodium serve as counterions in aluminum hydroxycarbonate gel. However, sodium could not be removed from dihydroxyaluminum sodium carbonate by exchange with magnesium because sodium is part of the crystal structure. It is hypothesized that aluminum hydroxycarbonate gels which resist removal of sodium are actually mixtures containing dihydroxyaluminum sodium carbonate in addition to aluminum hydroxycarbonate.

Keyphrases □ Aluminum hydroxycarbonate gel—removal of sodium by magnesium □ Counterions—removal of sodium by magnesium in aluminum hydroxycarbonate gel

Structural studies have suggested (1, 2) that the acid-reactive aluminum hydroxide gel used in antacids has a planar structure in which the basic unit is a six-membered ring of aluminum atoms joined by double hydroxide bridges. Carbonate is specifically adsorbed at aluminum sites along the edge (3-5). This structure suggests that other cations which may be present simply function as counterions. To further test the structural model of aluminum hydroxycarbonate gel, the ability of magnesium ions to replace sodium ions was studied.

EXPERIMENTAL SECTION

The aluminum hydroxycarbonate gel was precipitated by reacting solutions of 0.5 M aluminum chloride and 2.0 M sodium carbonate at a constant pH of 7.0 (6). A gel composed of a mixture of aluminum hydroxycarbonate and dihydroxyaluminum sodium carbonate was precipitated from the same system at a constant pH of 8.5 (6).

Each gel was divided into two equal portions. One portion, designated as the control, was washed with distilled water by adding a volume of distilled water equal to the volume of the gel, mixing for 15 min, and centrifuging to produce a clear supernatant. The supernatant was tested for chloride by the silver nitrate test (7). The washing procedure was repeated until the supernatant was free of chloride as indicated by the silver nitrate test. The second portion was washed four times with a volume of 1 M $MgCl_2$, which was equal to the volume of the gel before washing with distilled water as described above, and is called the magnesium-exchanged portion.

The chloride-containing aluminum hydroxide gel was prepared by treating 0.5 M $AlCl_3$ with 1 M KOH (8). The equivalent aluminum oxide and magnesium content were determined by chelatometric titration (9).

The sodium content was determined by atomic absorption spectrometry[1]. A sample containing a 0.4-g equivalent of aluminum oxide was dissolved by adding 4 mL of 12 M HCl. Potassium chloride (95 mg) was added, and the final volume was adjusted to 25 mL with distilled water. Standards and blanks for the magnesium-exchanged samples contained the same quantity of magnesium ion as was present in the sample.

IR spectra[2] were recorded on air-dried samples with potassium bromide pellets (0.75-mg sample and 300 mg of KBr). X-ray diffractograms were obtained with air-dried samples in powder mounts (McCreery mounts). Diffractograms were recorded from 6 to 40° (2θ) under the following conditions[3]: CuK_α radiation, 30 kV, 28 mA, 2°/min. The acid neutralization reaction was monitored by an automated[4] pH-stat titration (10). The point of zero charge was determined by a continuous titration procedure (8).

RESULTS AND DISCUSSION

The control and magnesium-exchanged portions of the aluminum hydroxycarbonate gel each required four washings with distilled water to produce a negative test for chloride. The control contained 0.82 M (8.4%) equivalent aluminum oxide and 2.5×10^{-2} M (0.057%) sodium, which is equivalent to a sodium-aluminum molar ratio of 1.5×10^{-2}. The magnesium-exchanged portion contained 0.78 M (8.0%) equivalent aluminum oxide and 2.7×10^{-3} M (0.0062%) sodium, which is equivalent to a sodium-aluminum molar ratio of 1.7×10^{-3}. Thus, ~90% of the sodium present in the control was removed by the magnesium-exchange procedure.

The IR spectrum and X-ray diffraction pattern of the magnesium-exchanged portion were typical of aluminum hydroxycarbonate gel (11) and were identical with the control (Fig. 1A and B), indicating that no structural changes occurred due to the magnesium-exchange procedure.

The control aluminum hydroxycarbonate gel was free of magnesium, whereas the magnesium-exchanged portion contained 6.9×10^{-2} M (0.17%) magnesium, which is equivalent to a magnesium-aluminum molar ratio of 0.044. Thus, as suggested by recent structural studies (1-5), sodium appears to be a counterion in aluminum hydroxycarbonate gel and not a structural component.

It should be noted that the sodium content of the control was low in terms of the clinical use of aluminum hydroxycarbonate gel as an antacid. For example, if the control were used at a dosage regimen of 40 mEq/dose for seven daily doses, as occurs in high-intensity antacid therapy (12, 13), the aluminum hydroxycarbonate gel would contribute 32 mg of sodium/d to the sodium intake of the patient. This represents only 6.4% of the 500 mg (22 mmol) of sodium allowed in a strict sodium-restricted diet (14). The magnesium-exchanged aluminum hydroxycarbonate gel would only contribute 3.7 mg of sodium/d for the same dosage regimen (<1% of the sodium allowed in a strict sodium-restricted diet).

The ratio of milliequivalents of magnesium adsorbed to milliequivalents of sodium desorbed was 6.2. This ratio exceeds the expected value of 1. It is hypothesized that magnesium displaced some other cation, such as a proton, in addition to sodium. Magnesium ions could displace protons in the diffuse portion of the electrical double layer or perhaps from the Stern layer.

The hypothesis that magnesium exchanges for protons in addition to sodium was tested by titrating a chloride-containing aluminum hydroxide suspension with magnesium nitrate. The pH of the chloride-containing aluminum hydroxide suspension and the 6×10^{-4} M $Mg(NO_3)_2$ was adjusted to 9.6, which is the point of zero charge for the chloride-containing aluminum hydroxide. This was necessary to eliminate pH shifts in the suspension on addition of titrant, which could be attributed to a simple ionic strength effect (8). The pH of the chloride-containing aluminum hydroxide suspension decreased from pH 9.6 to 8.76 as a result of titration with 3 mL of 6×10^{-4} M $Mg(NO_3)_2$ (Table I). Titration with 3 mL of water adjusted to pH 9.6 only caused a pH change of 0.08. The decrease in pH on addition of $Mg(NO_3)_2$ is believed to be due to the exchange of magnesium for protons at the aluminum hydroxide surface. Normally, the pH of the aluminum hydroxide at its point of zero charge would be unaffected by an ionic strength change since the background salt usually behaves as an indifferent electrolyte. This suggests that magnesium specifically adsorbs as a Stern layer ion and displaces protons in the process.

The antacid properties of the magnesium-exchanged aluminum hydroxycarbonate gel are very similar to the control. Both portions reacted completely within 15 min, with the neutralization of three protons per aluminum ion. Thus, the presence of sodium as a counterion in aluminum hydroxycarbonate

[1] Model 290B; Perkin-Elmer Co., Norwalk, Conn.
[2] Model 180; Perkin-Elmer Co., Norwalk, Conn.
[3] Siemens A G Kristalloflex 4 generator, Type F diffractometer; Karlsrule, Federal Republic of Germany.
[4] PHM 26, TTT 60, ABU 12 (2.5 mL), TTA60, REA 160; Radiometer, Copenhagen, Denmark.

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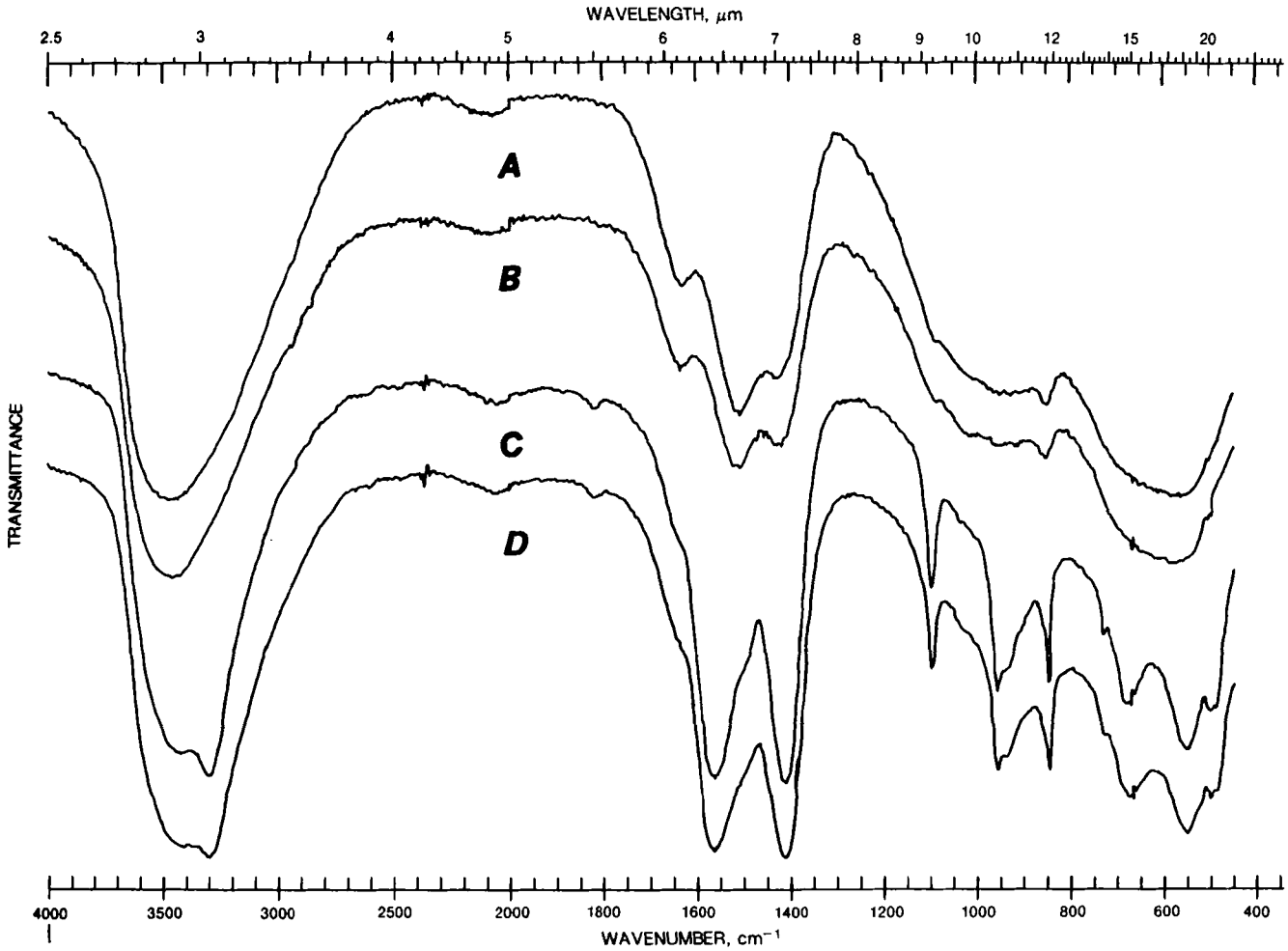

Figure 1—*IR spectra. Key: (A) control aluminum hydroxycarbonate gel; (B) magnesium-exchanged aluminum hydroxycarbonate gel; (C) control gel containing aluminum hydroxycarbonate gel and dihydroxyaluminum sodium carbonate; (D) magnesium-exchanged gel containing aluminum hydroxycarbonate gel and dihydroxyaluminum sodium carbonate.*

gel is unimportant in terms of antacid properties since the rate of acid neutralization is independent of sodium content (15).

The hypothesis that sodium is a counterion in aluminum hydroxycarbonate gel was further tested by attempting to exchange magnesium for sodium in a gel which is known to be a mixture of aluminum hydroxycarbonate and dihydroxyaluminum sodium carbonate. Dihydroxyaluminum sodium carbonate has the formula $NaAl(OH)_2CO_3$ and is known mineralogically as dawsonite (16). The precipitation conditions were altered to produce the desired mixture (6). The IR spectrum of the mixture (Fig. 1C) shows a wider split of the ν_3 mode of carbonate (1560 and 1410 cm^{-1}) than aluminum hydroxycarbonate (Fig. 1A). The IR spectrum of the mixture also contains bands which are characteristic of dawsonite at 3290, 1818, 955, 935, 846, and 550 cm^{-1} (17), in addition to the bands associated with aluminum hydroxycarbonate.

Table I—Titration of Aluminum Hydroxide [a] with 6×10^{-4} M Magnesium Nitrate

Sample[b]		Blank[b]	
pH	Titrant, mL	pH	Water, mL
9.60	0	9.63	0
9.52	0.1	9.61	0.1
9.44	0.2	9.60	0.5
9.36	0.3	9.58	1.0
9.30	0.4	9.56	2.0
9.21	0.6	9.55	3.0
9.12	0.8		
9.05	1.0		
8.96	1.4		
8.86	2.0		
8.76	3.0		

[a] At pH equal to the point of zero charge (9.6). [b] Aluminum hydroxide gel (100 mL) containing 1% equivalent aluminum oxide.

The sodium to aluminum molar ratio of the mixture was 0.50 after washing with water. The high sodium to aluminum molar ratio is due to the presence of dawsonite, which has a sodium-aluminum molar ratio of 1. The sodium-aluminum molar ratio of the mixture only decreased to 0.42 after magnesium exchange. It is believed that the sodium associated with aluminum hydroxycarbonate was exchanged with magnesium, but the sodium in dawsonite is part of the crystal structure and was not exchanged with magnesium.

In conclusion, cations such as sodium which are present in aluminum hydroxycarbonate gel function as counterions and can be removed by cation exchange. However, sodium cannot be removed by cation exchange from dihydroxyaluminum sodium carbonate. Thus, aluminum hydroxycarbonate gels which resist the removal of sodium by cation exchange may also contain dihydroxyaluminum sodium carbonate (dawsonite).

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Rapid Quantitative Liquid Chromatographic Determination of Caffeine Levels in Plasma after Oral Dosing

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Abstract □ A simple method is described for the rapid, quantitative analysis of caffeine in human plasma. Caffeine levels present in plasma following drug administration were determined by high-performance liquid chromatography with UV detection at 273 nm after plasma protein precipitation. Caffeine was detectable at levels as low as 0.1 μg/mL. Mean recoveries of 98% with a coefficient of variation of 3% were obtained for plasma standards, in which concentrations ranged from 0.1 to 8 μg/mL. Interassay variability of the slope of the standard curve had a coefficient of variation of 3%. Application of this method during human bioavailability studies is described.

Keyphrases □ Caffeine—HPLC, human plasma, bioavailability □ Bioavailability—caffeine, HPLC, human plasma, oral dosing

Caffeine is a commonly ingested drug that is present in foods, beverages, and medicaments. Its widespread use has stimulated an interest in the development of a simple and rapid plasma determination for caffeine suitable for analyzing multiple samples.

Although GC (1-3) and spectrophotometric (4) methods exist for caffeine determination in biological fluids, high-performance liquid chromatographic (HPLC) methods are relatively few, and those available suffer from the disadvantages of inadequate sensitivity (5), time-consuming extraction steps (5-7), dedicated equipment (8), inadequate sample cleanup, inadequate sensitivity for pharmacokinetic studies (9-11), and insufficient testing in human plasma (11).

The method described herein involves a single plasma protein precipitation followed by liquid chromatographic determination of caffeine in the clear supernatant. The plasma proteins were denatured and precipitated with 0.15 M $Ba(OH)_2$ and 5% $ZnSO_4$ solutions, as described previously (12). The use of this combination of reagents results in a supernatant with a neutral pH and a clean chromatographic profile due to efficient coprecipitation of both plasma proteins and excess reagents. The method is capable of detecting at least 0.1 μg/mL of caffeine, and the reproducibility eliminates the need for an internal standard. Furthermore, the ease and rapidity of sample workup make this method ideal for multiple-sample analyses.

This method has been used routinely on long-term human bioavailability studies, resulting in clean predose plasma chromatograms with no interference and no column deterioration after several hundred analyses, and has been found to be precise and accurate.

EXPERIMENTAL SECTION

Reagents—Standard solutions were prepared in distilled water. The 0.15 M $Ba(OH)_2$ and 5% $ZnSO_4$ solutions were obtained commercially[1].

Instrumentation and Operating Conditions—The analysis was performed with a high-performance liquid chromatograph[2] with a variable-wavelength UV detector[3] set at 273 nm, an automated injection system[4] fitted with a 75-μL loop, and a 30 cm × 4-mm i.d. reverse-phase, high-efficiency C_{18} col-

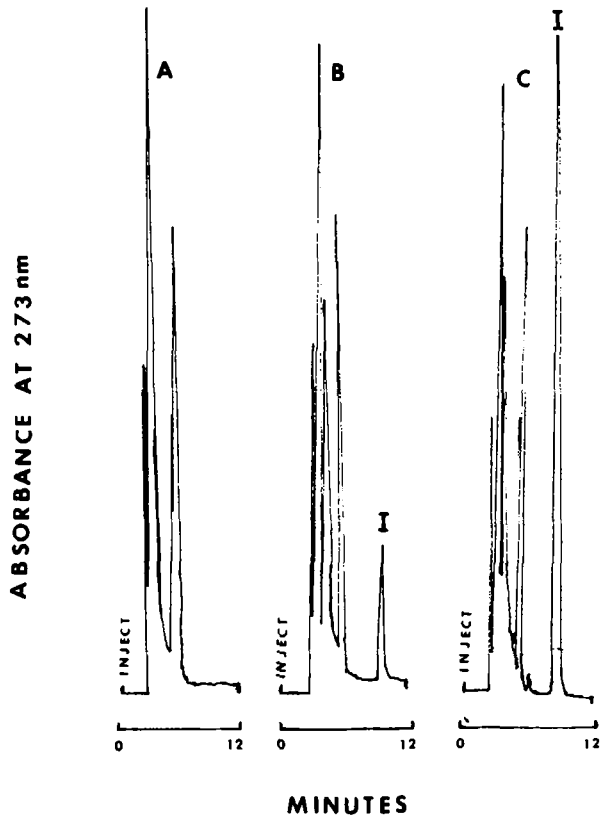

Figure 1—*Chromatograms for a typical subject. Key: (A) taken prior to caffeine (I) administration; (B) taken 10 min after oral administration of two 65-mg tablets; (C) taken 20 min postdose.*

[1] $ZnSO_4$ solution (lot SO-Z-10), $Ba(OH)_2$ solution (lot SO-B-138); Fisher Scientific Co.
[2] Model 6000; Waters Associates, Milford, Mass.
[3] Model 773; Kratos, Ramsey, N.J.
[4] Model 725; Mircomeritics, Norcross, Ga.

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