

# Structural Survey of Carbonate-Containing Antacids

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**Abstract** □ A series of carbonate-containing antacids was examined by IR and X-ray analysis to establish the role of carbonate and to compare the structure of the antacids to naturally occurring carbonate minerals. Based on IR analysis, the relative degree of perturbation of carbonate increases in the order calcium carbonate, carbonate-containing aluminum hydroxide gel, and dihydroxyaluminum sodium carbonate. The crystalline carbonate-containing antacids were poorly organized forms of the minerals calcite,  $\text{CaCO}_3$ ; dawsonite,  $\text{NaAl}(\text{OH})_2\text{CO}_3$ ; and hydrotalcite,  $\text{Mg}_6\text{Al}_2\text{CO}_3(\text{OH})_{16}\cdot 4\text{H}_2\text{O}$ . Amorphous carbonate-containing aluminum hydroxide gel can be classified mineralogically as amorphous aluminum hydroxycarbonate. IR and X-ray evidence indicates that magaldrate has a hydrotalcite-like structure with sulfate as the major interlayer anion and carbonate also present in the interlayer space.

**Keyphrases** □ Antacids, various carbonate containing—IR and X-ray structural analysis, compared to naturally occurring carbonate minerals □ Carbonate-containing antacids, various—IR and X-ray structural analysis, compared to naturally occurring carbonate minerals □ Structural analysis, IR and X-ray—various carbonate-containing antacids, compared to naturally occurring carbonate minerals

An examination of the composition of the most widely used antacids indicates that carbonate is a common component. Crystalline carbonates are exemplified by calcium carbonate, dihydroxyaluminum sodium carbonate, and magnesium aluminum hydroxycarbonate (1), while amorphous carbonates are represented by carbonate-containing aluminum hydroxide gel. Although the name aluminum hydroxide gel does not suggest the presence of carbonate, the USP recently recognized that carbonate may be present in aluminum hydroxide gel (2).

Recent reports showed that carbonate is covalently bonded to aluminum in aluminum hydroxide gel (3) and that carbonate plays an important role in acid neutralization (4) as well as in stabilization of the gel (5). These carbonate-containing antacids were studied by IR spectroscopy and X-ray diffraction to examine the role of carbonate in these diverse antacid compounds and to compare the structure of carbonate-containing antacids to naturally occurring carbonate minerals.

## EXPERIMENTAL

Commercial antacid dosage forms were used. Aluminum hydroxide gel was examined in a suspension dosage form<sup>2</sup> labeled as a magnesia and alumina oral suspension. Calcium carbonate was studied in a tablet<sup>3</sup> containing 500 mg of calcium carbonate. Dihydroxyaluminum sodium carbonate was obtained as a tablet<sup>4</sup> containing 334 mg of dihydroxyaluminum sodium carbonate. An antacid suspension<sup>5</sup> was the source of magaldrate.

A commercial sample of aluminum hydroxide<sup>6</sup> was examined.

Mineralogical specimens were studied to establish the structure of the carbonate-containing antacids. Naturally occurring samples of dawsonite<sup>7</sup>,  $\text{NaAl}(\text{OH})_2\text{CO}_3$ , and hydrotalcite<sup>8</sup>,  $\text{Mg}_6\text{Al}_2\text{CO}_3(\text{OH})_{16}\cdot 4\text{H}_2\text{O}$ ,

were included. The X-ray diffractograms of all mineral specimens were compared to the ASTM Diffraction Data File and found to be of high purity.

The commercial antacids were examined as purchased by X-ray diffraction, using the Debye-Scherrer method, and by IR spectroscopy, using potassium bromide pellets containing 1–7 mg of sample/300 mg of potassium bromide.

The calcium carbonate, dihydroxyaluminum sodium carbonate, and magaldrate dosage forms were examined after several washings with water to remove excipients. Magaldrate suspension was studied by IR spectroscopy under vacuum ( $10^{-4}$  mm Hg) and after deuterium exchange under vacuum ( $10^{-4}$  mm Hg) at 25°.

## RESULTS AND DISCUSSION

**Aluminum Hydroxide Gel**—IR and X-ray analysis of the aluminum hydroxide gel–magnesium hydroxide gel antacid indicates that the product is a physical mixture of amorphous carbonate-containing aluminum hydroxide gel and crystalline magnesium hydroxide. A comparison of the IR spectrum of the product with synthetic magnesium hydroxide (brucite) and amorphous carbonate-containing aluminum hydroxide gel is shown in Fig. 1.

The broad absorption band centered at  $3440\text{ cm}^{-1}$  is due to the hydroxyl stretching vibrations of aluminum hydroxide. The diffuse nature of this band indicates that the hydroxyls are in many different environments. The two bands at  $1500$  and  $1435\text{ cm}^{-1}$  are due to the splitting of the carbonate band that appears at  $1415\text{ cm}^{-1}$  when carbonate is unperturbed (3). This finding is corroborated by the presence of the absorption band at  $1090\text{ cm}^{-1}$ , which only becomes IR active when the symmetry of the carbonate anion is lowered.

The magnitude of the splitting of the degenerate  $\nu_3$  vibration of the carbonate anion in the aluminum hydroxide gel,  $65\text{ cm}^{-1}$ , indicates a unidentate coordination with the aluminum hydroxide polycations (6). The band at  $850\text{ cm}^{-1}$  is the  $\nu_2$  vibration of the carbonate anion and is shifted from its unperturbed frequency of  $879\text{ cm}^{-1}$ .

Absorption bands in the IR spectrum of aluminum hydroxide gel at  $1640$  and  $600\text{ cm}^{-1}$  can be assigned to molecular water and Al–O vibrations, respectively (7).

No reported minerals are amorphous and possess the same IR spectrum as carbonate-containing aluminum hydroxide gel. However, Duffin and Goodyear (8) reported on scarbroite, a crystalline aluminum hydroxycarbonate with the formula  $\text{Al}_2(\text{CO}_3)_3\cdot 12\text{Al}(\text{OH})_3$ . The IR spectrum of scarbroite is similar to that of carbonate-containing aluminum hydroxide gel (Fig. 1C); the difference between carbonate-containing aluminum hydroxide gel and scarbroite probably is particle size. Scarbroite has been found associated with gibbsite, which is the final crystalline form in the aging of aluminum hydroxide gel.

The remaining bands observed in the IR spectrum of the aluminum hydroxide gel–magnesium hydroxide gel dosage form arise from magnesium hydroxide (Fig. 1B). The IR spectrum of the magnesium hydroxide gel identifies it as crystalline magnesium hydroxide,  $\text{Mg}(\text{OH})_2$ , known mineralogically as brucite. The well-ordered crystalline lattice is indicated by sharp absorption bands, especially for the stretching and libration vibrations of the hydroxyls at  $3700$  and  $360\text{ cm}^{-1}$ , respectively, which indicate the electrostatic nature of the hydroxyl groups (9). Absorption bands at  $565$  and  $445\text{ cm}^{-1}$  can be assigned to Mg–O vibrations (10).

The X-ray diffractogram of the aluminum hydroxide gel–magnesium hydroxide gel dosage form (Table I) is identical to brucite, indicating that the product is a physical mixture of amorphous aluminum hydroxide gel and crystalline magnesium hydroxide.

**Calcium Carbonate**—The IR spectrum of the calcium carbonate tablet is quite complex (Fig. 2). However, after the water-soluble excipients are removed by washing, the characteristic IR spectrum of the mineral calcite,  $\text{CaCO}_3$ , is observed. Absorption bands due to the carbonate ion occur at  $1440$ ,  $870$ , and  $710\text{ cm}^{-1}$ . A lattice vibration is seen at  $325\text{ cm}^{-1}$  (11).

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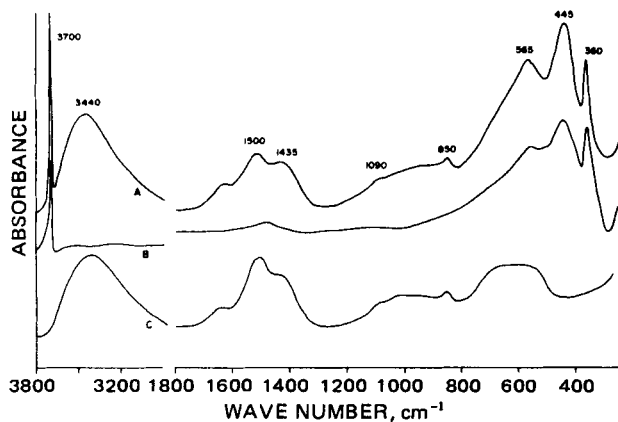


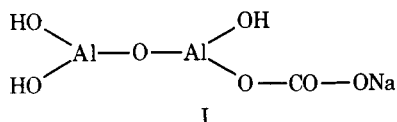
Figure 1—IR spectra of: A, magnesia and alumina oral suspension washed with water to remove excipients (2 mg/300 mg of potassium bromide); B, synthetic brucite,  $Mg(OH)_2$  (2 mg/300 mg of potassium bromide); and C, aluminum hydroxide gel (2 mg/300 mg of potassium bromide).

There are two other crystal forms of calcium carbonate: aragonite and vaterite. These forms can be distinguished easily from calcite by IR spectroscopy since the carbonate ion is asymmetrically distorted in both polymorphs. However, the carbonate ion in calcite is symmetrically perturbed by the electrostatic field generated by the nearest-neighbor environment. This symmetrical crystal field accounts for the difference in the IR spectra of the undistorted carbonate ion in solution and of calcite (Table II).

The X-ray diffractogram (Table I) clearly establishes that the mineral calcite is the form of calcium carbonate present in the antacid tablet.

**Dihydroxyaluminum Sodium Carbonate**—The IR spectrum (Fig. 3) of the dihydroxyaluminum sodium carbonate dosage form is identical to the IR spectrum of the mineral dawsonite,  $NaAl(OH)_2CO_3$ , except that the bands are broader for the dihydroxyaluminum sodium carbonate, which indicates a relatively less ordered structure or a smaller particle size. The relationship between dihydroxyaluminum sodium carbonate and dawsonite is also seen by X-ray diffraction (Table I).

Some confusion exists concerning dihydroxyaluminum sodium carbonate. Lewin (12) claimed to have synthesized an antacid with Structure I.



However, Lewin's IR spectra indicate that the synthetic compound is dawsonite. Lewin's material probably contained some amorphous aluminum hydroxide because the product had an aluminum to carbonate ratio greater than 1.

Seiyama *et al.* (13) showed that the hydrolysis of sodium aluminate with carbon dioxide is accompanied by the formation of dawsonite. However, because dawsonite was deposited below a critical pH at which

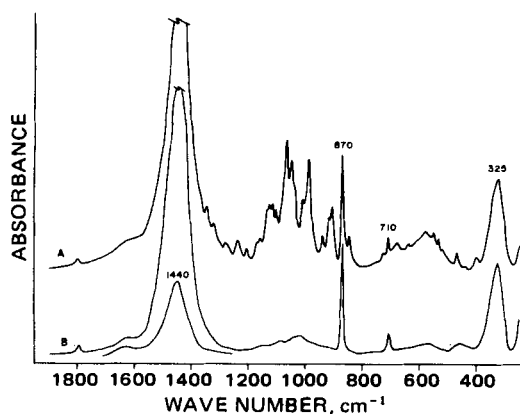


Figure 2—IR spectra of: A, calcium carbonate tablet (1.5 mg/300 mg of potassium bromide); and B, calcium carbonate tablet washed with water to remove excipients (1.5 mg/300 mg of potassium bromide).

Table I—X-Ray Data of Carbonate-Containing Antacids and Carbonate-Containing Minerals

Magnesia and Alumina Oral Suspension		Brucite <sup>a</sup> $Mg(OH)_2$	
$d_{hkl}$	Intensity <sup>b</sup>	$d_{hkl}$	$I/I_1$
4.78	s	4.77	90
2.74	w	2.72	6
2.36	vs	2.36	100
Calcium Carbonate Tablet		Calcite <sup>a</sup> $CaCO_3$	
$d_{hkl}$	Intensity <sup>b</sup>	$d_{hkl}$	$I/I_1$
3.86	vw	3.86	12
3.04	vs	3.035	100
2.49	vw	2.495	14
2.29	w	2.28	18
2.09	w	2.09	18
1.91	w	1.91	17
1.87	w	1.87	17
Dihydroxyaluminum Sodium Carbonate		Dawsonite <sup>a</sup> $NaAl(OH)_2CO_3$	
$d_{hkl}$	Intensity <sup>b</sup>	$d_{hkl}$	$I/I_1$
5.7	vs	5.7	100
3.39	m	3.38	70
2.79	vs	2.79	90
2.50	m	2.50	50
2.15	m	2.15	60
1.98	m	1.98	80
Magaldrate Suspension		Magaldrate <sup>c</sup>	
$d_{hkl}$	Intensity <sup>b</sup>	$d_{hkl}$	$I/I_1$
7.75	vs		
3.83	s		
2.57	m	2.57	95
2.32	m	2.30	55
1.95	w	1.97	33
		1.52	100
		1.49	65
		1.41	10
		1.31	10
		1.265	12
		0.992	6
		0.973	8
		0.876	10
		Hydrotalcite <sup>a</sup> $Mg_6Al_2CO_3(OH)_{16} \cdot 4H_2O$	
$d_{hkl}$		$d_{hkl}$	$I/I_1$
7.84			100
3.90			60
2.60			40
2.33			25
1.990			30
1.541			35
1.498			25
1.419			8
1.302			6
1.265			10
0.994			4
0.976			6

<sup>a</sup> Taken from ASTM Diffraction Data File. <sup>b</sup> Estimated intensity from diffractogram: vs = very strong, s = strong, m = medium, w = weak, and vw = very weak. <sup>c</sup> From Ref. 20.

the bicarbonate-ion concentration in solution begins to increase, the formula  $NaAlOOH HCO_3$  was assigned. The IR spectrum of dawsonite does not agree with the presence of bicarbonate ion. Rather the IR spectrum indicates the presence of distorted carbonate ion.

The crystal structure of dawsonite, as determined by Frueh and Golithly (14), places carbonate in a lower site of symmetry than the unperturbed carbonate ion ( $D_3h$ ). Consequently, the absorption bands at 1575 and 1390  $cm^{-1}$  are due to the removal of the degeneracy of the  $\nu_3$  mode of carbonate; this finding is supported by the appearance of the  $\nu_1$  mode at 1095  $cm^{-1}$ , which is IR inactive in unperturbed carbonate. The other vibrations of carbonate in dawsonite are indicated in Table II.

The absence of the characteristic water vibration at 1640  $cm^{-1}$  from the IR spectra of both dihydroxyaluminum sodium carbonate and dawsonite indicates that molecular water is not present. This result is in disagreement with the formula of dihydroxyaluminum sodium carbonate

**Table II—IR Absorption Bands of Carbonate Ion in Different Carbonate-Containing Antacids**

	Wave Number, cm <sup>-1</sup>				
	Carbo- nate Ion in Solution	Calcium Carbo- nate (Calcite)	Alumi- num Hydrox- ide Gel	Dihydroxy- aluminum Sodium Carbonate (Dawsonite)	Hydro- talcite
$\nu_1(A_1')$ , R	—	—	1090	1095	1105 <sup>a</sup>
$\nu_2(A_2')$ , IR	879	870	850	842	— <sup>b</sup>
$\nu_3(E')$ , IR, R	1415	1440	1435	1390	1390 <sup>c</sup>
			1500	1575	(1640) <sup>d</sup>
$\nu_4(E')$ , IR, R	680	710	— <sup>b</sup>	727	— <sup>b</sup>
			— <sup>b</sup>	— <sup>b</sup>	

<sup>a</sup> In magaldrate, this absorption is very intense due to the presence of sulfate.  
<sup>b</sup> Not observed. <sup>c</sup> May be observed as a doublet. <sup>d</sup> Due to bicarbonate ion.

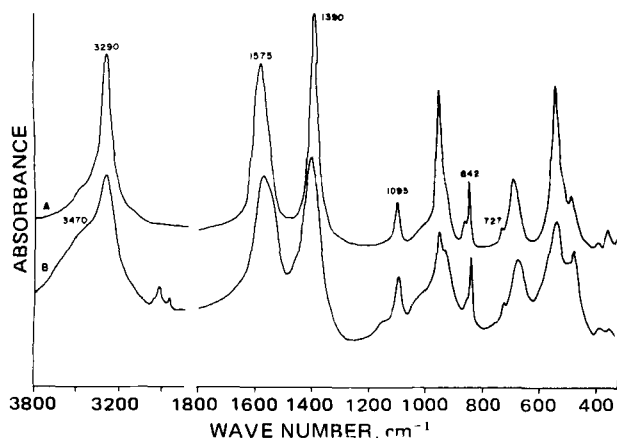
given in the NF (15). Furthermore, the formula  $\text{CH}_2\text{AlNaO}_5 \cdot x\text{H}_2\text{O}$  given in the NF does not clearly indicate the presence of carbonate and is not as useful as the mineralogical formula,  $\text{NaAl(OH)}_2\text{CO}_3$ .

Other crystalline hydroxycarbonates similar to dawsonite have been prepared. Potassium aluminum hydroxycarbonate and ammonium aluminum hydroxycarbonate were shown to have excellent antacid properties (16, 17).

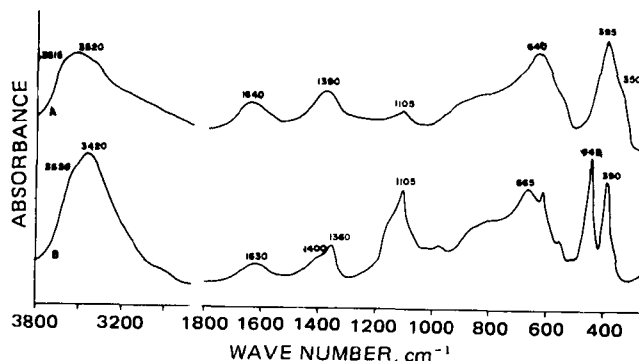
**Hydrotalcite**—Hydrotalcite is a variety of the pyroaurite-sjögrenite group of minerals with the general formula  $\text{M}^{2+}_6\text{M}^{3+}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$  in which the divalent cation is magnesium and the trivalent cation is aluminum (18). Three-dimensional structural analysis has not been performed on hydrotalcite; however, a one-dimensional structural analysis was interpreted in terms of a structure consisting of brucite layers alternating with hydrous aluminum layers bearing carbonate (19).

A somewhat different structure, proposed by Brown and Gastuche (20), consists of positively charged brucite-like layers in which aluminum replaces magnesium up to a maximum of about one in three sites. The positive charge is balanced by an interlayer sheet containing carbonate ion and water molecules. This structure seems more probable and can explain the differences in the  $d_{hkl}$  values found in several hydrotalcites (1, 19, 20). In addition, hydrotalcite-like structures in which the carbonate ion is totally or partially replaced by other anions such as nitrate, sulfate, perchlorate, or chloride were synthesized (21, 22).

The X-ray diffractogram of natural hydrotalcite is presented in Table I, and the IR spectrum is given in Fig. 4A. The absorption band at 1640  $\text{cm}^{-1}$  is not due solely to molecular water since it is not significantly affected by deuterium exchange. This finding indicates that absorption bands at 1640 and 1400  $\text{cm}^{-1}$  are due to the vibrations of carbonate groups. Since the carbonate anions are between layers in the Brown-Gastuche structure, it seems unlikely that a splitting in the  $\nu_3$  vibration of greater magnitude than that observed in dawsonite will occur. Therefore, it is suggested that bicarbonate ions may be present together with carbonate ions in hydrotalcite. The absorption bands at 1640 and 1400  $\text{cm}^{-1}$  may be due to bicarbonate and carbonate, respectively. A slight splitting (1400–1360  $\text{cm}^{-1}$ ) of the carbonate  $\nu_3$  vibration occurred when hydrotalcite was evacuated, which may be due to an interaction of carbonate with the Mg–Al sheets.



**Figure 3**—IR spectra of: A, natural dawsonite,  $\text{NaAl(OH)}_2\text{CO}_3$  (2 mg/300 mg of potassium bromide); and B, dihydroxyaluminum sodium carbonate tablet washed with water to remove excipients (2 mg/300 mg of potassium bromide).



**Figure 4**—IR spectra of: A, natural hydrotalcite,  $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$  (2 mg/300 mg of potassium bromide); and B, magaldrate suspension washed with water to remove excipients (2 mg/300 mg of potassium bromide).

Figure 5 shows a schematic representation of the hydrotalcite structure. The positive charge created by the substitution of aluminum for magnesium is compensated by the negatively charged interlayer carbonate, bicarbonate, and hydroxyl ions.

Hydrotalcite,  $\text{Mg}_6\text{Al}_2(\text{OH})_{16}\text{CO}_3 \cdot 4\text{H}_2\text{O}$ , was synthesized (1) and its antacid properties were investigated (23).

The USP (24) defines magaldrate as a chemical combination of aluminum hydroxide and magnesium hydroxide, corresponding approximately to the formula  $\text{Al}_2\text{H}_{14}\text{Mg}_4\text{O}_{14} \cdot 2\text{H}_2\text{O}$ . The USP does not contain X-ray diffraction data on magaldrate, although a table of  $d$ -spacings was included in NF XIII (25). The NF diffraction pattern is given in Table I along with the diffractograms of the magaldrate dosage form and a natural hydrotalcite.

It is surprising that the two strong reflections at 7.75 and 3.83 Å present in the magaldrate dosage form are not included in the NF reference standard. The other reflections match up very well and would do so in terms of relative intensity if the reflection at 7.75 Å were taken as 100. A comparison of the X-ray spacing of the magaldrate dosage form and hydrotalcite clearly indicates that magaldrate has a hydrotalcite-like structure.

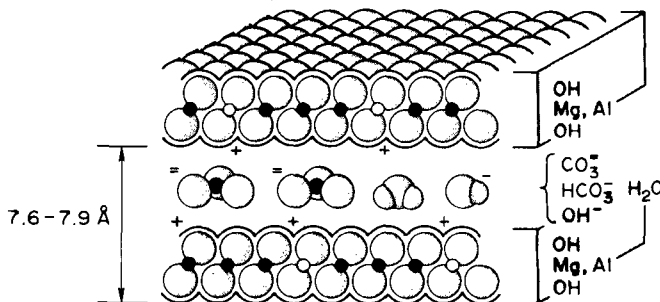
The IR spectra of several synthetic and natural hydrotalcite-type minerals were reported (1, 19, 26, 27), although no band assignments were made. Figure 4 presents the IR spectra of magaldrate and a natural hydrotalcite. Although the IR spectra of both samples are similar, some differences appear in the 1400- and 800–350- $\text{cm}^{-1}$  regions. The differences in the 800–350- $\text{cm}^{-1}$  region may be understood based on the structure proposed by Brown and Gastuche (20). Hydrotalcite-like structures can accommodate different aluminum to magnesium ratios, which could result in the observed spectral differences since vibrations in the 800–350- $\text{cm}^{-1}$  region are probably due to Al–O and Mg–O vibrations of the octahedral sheets.

The differences between magaldrate and natural hydrotalcite at 1400  $\text{cm}^{-1}$  are more apparent than real since evacuation of the natural hydrotalcite produced the splitting observed in the magaldrate sample.

A significant difference between the IR spectrum of magaldrate and natural hydrotalcite is the strong absorption band at 1105  $\text{cm}^{-1}$  in magaldrate. Absorption bands in this spectral region are characteristic of sulfate anion, which may be the major interlayer anion in magaldrate.

### SUMMARY

The carbonate-containing antacids present a wide spectrum of structural arrangements of carbonate. This is seen most clearly if the IR car-



**Figure 5**—Schematic representation of hydrotalcite.

bonate bands are compared (Table II). The carbonate bands observed in the calcium carbonate antacid are very similar to those of the unperturbed carbonate ion, indicating a symmetrical arrangement of carbonate in the crystal structure.

A significant perturbation of the carbonate IR absorption bands was observed in carbonate-containing aluminum hydroxide gel, reflecting the coordination of carbonate to aluminum in the amorphous structure. The splitting of the  $\nu_3$  vibration suggests a unidentate interaction with aluminum. Carbonate is perturbed to a greater degree in dihydroxyaluminum sodium carbonate, suggesting a bidentate coordination for the carbonate ion. This is in good agreement with the crystal structure of dawsonite.

IR evidence suggests that both carbonate and bicarbonate are interlayer anions in hydrotalcite.

Based on IR and X-ray analysis, magaldrate has a hydrotalcite-like structure with sulfate as the major interlayer anion and carbonate present in the interlayer space. The evidence does not support the present identification of magaldrate as a magnesium aluminum hydroxide.

The relationship between the carbonate-containing compounds used as antacids and natural minerals is also apparent based on this study. Amorphous carbonate-containing aluminum hydroxide gel can be classified mineralogically as amorphous aluminum hydroxycarbonate. The crystalline carbonate-containing antacids are somewhat poorly organized forms of the minerals calcite,  $\text{CaCO}_3$ ; dawsonite,  $\text{NaAl}(\text{OH})_2\text{CO}_3$ ; and hydrotalcite,  $\text{Mg}_6\text{Al}_2\text{CO}_3(\text{OH})_{16}\cdot 4\text{H}_2\text{O}$ .

Based on these findings, it is suggested that the official definitions should recognize that: (a) carbonate is coordinated to aluminum in the aluminum hydroxide gel structure; (b) dihydroxyaluminum sodium carbonate is a synthetic form of the mineral dawsonite and the mineralogical formula  $\text{NaAl}(\text{OH})_2\text{CO}_3$  should be used rather than the present official formula,  $\text{CH}_2\text{AlNaO}_5\cdot x\text{H}_2\text{O}$ , since no molecular water is present and the official formula does not clearly indicate that the compound is a hydroxycarbonate; and (c) magaldrate has a hydrotalcite-like structure.

It is believed that an understanding of the structural relationship between carbonate-containing antacids will lead to improved methods for the production and control of the antacids and will provide a useful framework for the development of new antacids.

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# Kinetics of Digoxin Stability in Aqueous Solution

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**Abstract** □ Digoxin hydrolysis was studied as a function of pH. Conversion of digoxin to digoxigenin was followed by high-pressure liquid chromatography and shown to proceed by the initial loss of one, two, or three sugars. The hydrolysis rate was directly proportional to parent drug concentration and hydrogen-ion activity. The individual hydrolysis rate constants of digoxin, digoxigenin bisdigitoxoside, and digoxigenin monodigitoxoside were determined by a simplex fitting procedure. Data are presented suggesting that at least some variation in the bioavailability of orally administered digoxin arises from observed variations in gastric

pH; these variations influence the extent to which hydrolysis occurs and, thus, modify the composition of digoxin species available for absorption.

**Keyphrases** □ Digoxin—hydrolysis, kinetic study, effect of pH □ Hydrolysis—digoxin, kinetic study, effect of pH □ Kinetics—digoxin hydrolysis, effect of pH □ Stability—digoxin in aqueous solution, kinetic study of hydrolysis, effect of pH □ Cardiotonic agents—digoxin, hydrolysis, kinetic study, effect of pH

Digoxin is a widely prescribed glycoside used in the maintenance therapy of cardiac patients. Significant variability has been observed in the efficiency with which

digoxin is absorbed from the GI tract among patients given the drug orally. Moreover, significant variations in bioavailability were noted within individual patients (1, 2).