

In summary, the present study has shown that the use of GC with electron-capture detection improves, to a large extent, the sensitivity of the previous HPLC and GC methods. This procedure is appropriate for monitoring plasma levels during single-dose pharmacokinetic studies.

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Desorption of Carbonate from Aluminum Hydroxycarbonate Gel by Nitrogen Purging

EDWARD C. SCHOLTZ*, JOSEPH R. FELDKAMP ‡,
JOE L. WHITE †, and STANLEY L. HEM**

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Abstract □ Carbonate was completely desorbed from amorphous aluminum hydroxycarbonate gel by purging with nitrogen. The reversibility of carbonate adsorption suggests that aluminum hydroxycarbonate particles are composed of planes of aluminum hydroxide with carbonate adsorbed at edge aluminum sites. A slow-reacting phase which was identified as a precursor of gibbsite, formed when the carbonate/aluminum molar ratio was <0.20.

Keyphrases □ Desorption—carbonate from aluminum hydroxycarbonate gel, nitrogen purging □ Carbonate—desorption from aluminum hydroxycarbonate gel, nitrogen purging □ Nitrogen purging—desorption of carbonate from aluminum hydroxycarbonate gel □ Aluminum hydroxycarbonate gel—desorption of carbonate, nitrogen purging

The coordination of carbonate by aluminum in aluminum hydroxide has been demonstrated by Raman and IR analyses (1–3) as well as by the effect of carbonate adsorption on the point of zero charge of aluminum hydroxide (4). The term specific adsorption describes the adsorption of carbonate by aluminum hydroxide as it refers to the adsorption of anions by the formation of a partial covalent bond with structural metal atoms and the

concomitant displacement of hydroxyl or water groups from the surface (5, 6).

The importance of specifically adsorbed carbonate in maintaining the structure and antacid properties of aluminum hydroxide gel has been demonstrated by numerous kinetic studies (3, 7–11). Insight into adsorption mechanisms may be gained by studying desorption reactions. Hingston *et al.* (12) found that specific adsorption of phosphate, selenite, and fluoride by gibbsite or goethite varied between complete reversibility and almost complete irreversibility. The reversibility of the specifically adsorbed anion was related to the nature of the adsorption complex. Adsorption was reversible when only unidentate ligands formed between the anion and metal, *i.e.*, fluoride anion. However, multidentate ligands, bridging, or the formation of ring structures at the surface led to irreversibility. McBride (13) concluded from spin probe studies that easily desorbed anions were adsorbed on aluminum hydroxide by ligand exchange of a single surface hydroxyl while anions that could not be easily desorbed were adsorbed by bidentate bonds. Gast (6) also suggested that readily desorbed anions have one coordinated bond to the surface while those more strongly retained have two coordinated bonds. Therefore, the desorption of specifically adsorbed carbonate from aluminum hydroxycarbonate gel was studied as part of efforts to improve the antacid properties and stability of antacid products.

EXPERIMENTAL

The two aluminum hydroxycarbonate gels (CG1 and CG2) studied were obtained commercially¹ as 9.5% equivalent Al₂O₃ pourable gels and were diluted with distilled water to 5% equivalent Al₂O₃. IR analysis² was

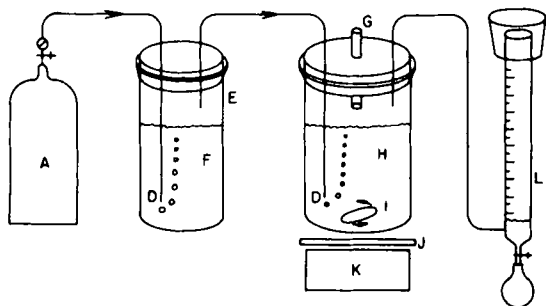


Figure 1—Apparatus for purging aluminum hydroxycarbonate gel with nitrogen gas. Key: (A) nitrogen gas cylinder; (E) glass cylinder; (D) fritted glass gas disperser; (F) water; (G) sealable sampling port; (H) aluminum hydroxycarbonate gel; (I) magnetic stirring bar; (J) heat shield; (K) magnetic stirrer; (L) soap bubble flow meter.

¹ Reheis Chemical Co., Berkeley Heights, N.J. and Chattem Chemical, Chattanooga, Tenn.

² Model 180; Perkin-Elmer Co., Norwalk, Conn.

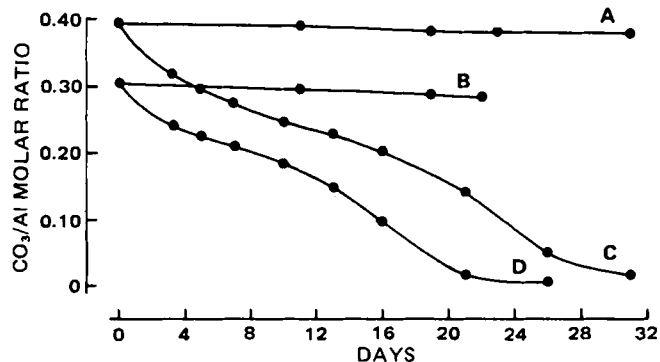


Figure 2—Change in the carbonate content of two commercial aluminum hydroxycarbonate gels during the nitrogen purge. Key: (A) CG1, control; (B) CG2, control; (C) CG1, nitrogen purge; (D) CG2, nitrogen purge.

performed on air-dried samples as potassium bromide pellets. Equivalent aluminum oxide content was determined by chelatometric titration (14).

Carbonate content was determined by a gasometric displacement technique (15) using the Chittick apparatus³. Because the addition of strong acid to aluminum hydroxycarbonate gel is an exothermic process, temperature control was required for accurate gas volume measurements. The Chittick reaction flask was immersed in a water bath maintained at room temperature, and the evolved carbon dioxide was passed through a copper coil (0.318 i.d. × 0.476 o.d. × 243 cm) inserted between the reaction flask and the measuring cylinder which was submerged in a water

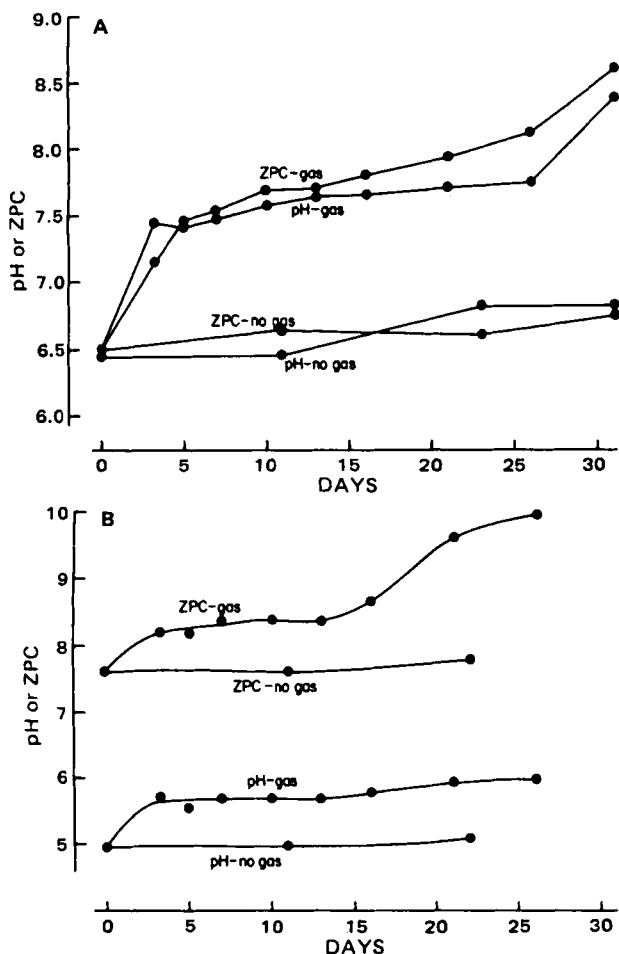


Figure 3—Change in the pH and point of zero charge (ZPC) of CG1 (A) and CG2 (B) during the nitrogen purge. Key: (gas) nitrogen purge; (no gas) control.

³ Sargent-Welch Scientific Co., Skokie, Ill.

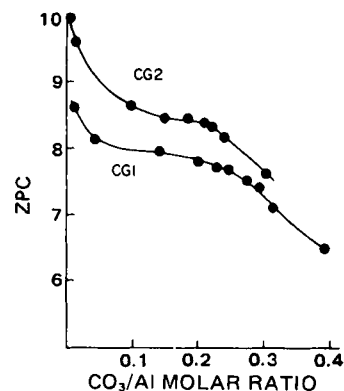


Figure 4—Change in the point of zero charge (ZPC) during carbonate desorption from two commercial aluminum hydroxycarbonate gels.

bath maintained at room temperature. The carbonate content was expressed as the carbonate-aluminum molar ratio.

The point of zero charge (ZPC) was determined by a continuous potentiometric titration procedure (4). The acid reactivity was determined by the pH-stat technique at pH 3, 25°C employing an automatic titration apparatus⁴ (16). X-ray powder diffractograms⁵ were obtained on air-dried samples under the following operating conditions: CuK_α radiation, 30 kV, 28 mA, 3 s time constant, 6–30° 2θ.

A diagram of the apparatus used to purge the aluminum hydroxycarbonate gels with nitrogen is shown in Fig. 1. The nitrogen was saturated with water by bubbling through water prior to contact with the sample, thus minimizing the drying of the gel. The nitrogen flow was maintained at 153 mL/min; the initial sample was 1100 mL. As a consequence of

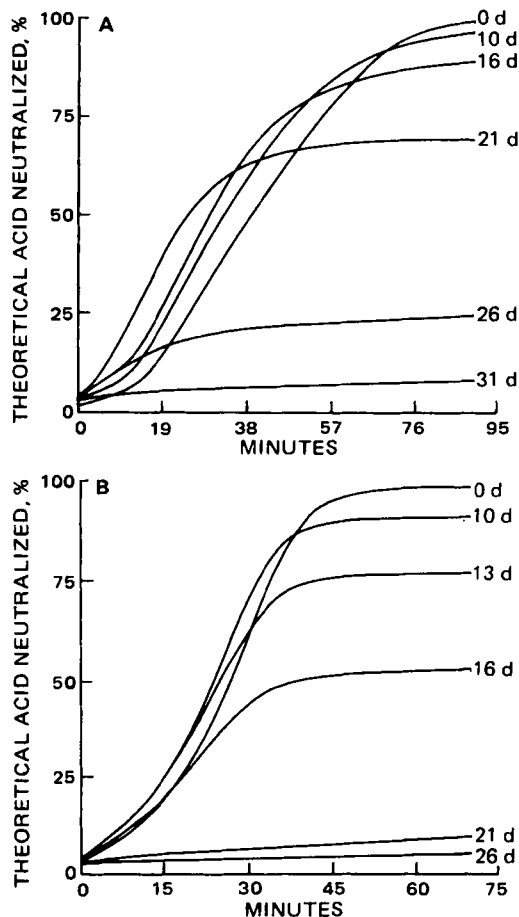


Figure 5—pH-stat titrations at pH 3, 25°C of CG1 (A) and CG2 (B) during nitrogen purging.

⁴ PHM 62, TTT 60, ABU 12 (2.5 mL), TTA 60, RFA 160; Radiometer, Copenhagen, Denmark.

⁵ Siemens Type F diffractometer; Siemens Corp., Iselin, NJ.

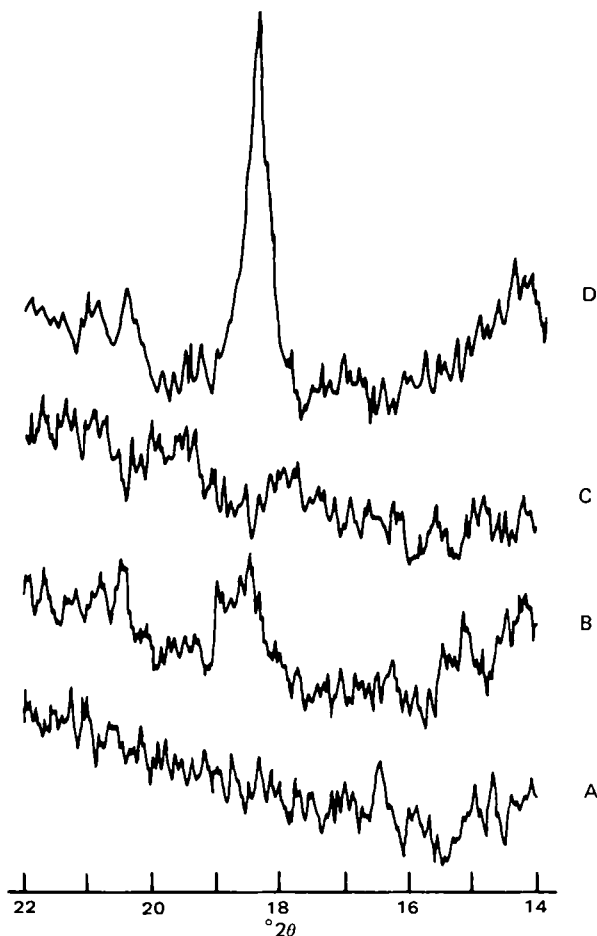


Figure 6—X-ray powder diffractograms of CG1 and CG2 following nitrogen purging. Key: (A) CG1 control and after 31 d of nitrogen purging; (B) CG1 after 31 d of nitrogen purging followed by 16 d of aging at room temperature; (C) CG2 control and after 26 d of nitrogen purging; (D) CG2 after 26 d of nitrogen purging followed by 7 d of aging at room temperature.

periodic sampling, ~350 mL remained at the end of the study. The control samples were not exposed to nitrogen and were stored in tightly sealed high-density polyethylene bottles at room temperature.

RESULTS AND DISCUSSION

The initial carbonate/aluminum molar ratios of CG1 and CG2 were 0.40 and 0.31, respectively. The IR spectrum of CG1 had absorption bands at 1510 and 1440 cm^{-1} and CG2 had absorption bands at 1505 and 1435 cm^{-1} , indicating that the carbonate was coordinated to aluminum (1–3). Further evidence of the specific adsorption of carbonate was provided by the point of zero charge (6.5 for CG1 and 7.6 for CG2) which was substantially lower than the 9–10 range reported for aluminum hydroxide (4).

Carbonate was readily removed from both aluminum hydroxycarbonate gels by purging with nitrogen (Fig. 2). Essentially complete carbonate removal was accomplished in 31 and 21 d for CG1 and CG2, respectively. The rate of desorption was similar. The only significant difference was the higher initial carbonate/aluminum molar ratio of CG1, which is a function of precipitation conditions and aging. The small loss of carbonate from the control samples indicates the inherent instability of aluminum hydroxycarbonate gels.

The complete removal of carbonate from the two aluminum hydroxycarbonate gels by nitrogen purging suggests that the carbonate sites are readily accessible, *i.e.*, edge sites. The complete removal of carbonate also suggests that adsorption is by unidentate rather than multidentate coordination (6, 12, 13). The same conclusion regarding unidentate coordination was reached based on the magnitude of the splitting of the degenerate ν_3 vibration of the carbonate anion in the IR spectrum of aluminum hydroxycarbonate gel (17). Thus, aluminum hydroxycarbonate

particles are believed to be composed of sheets of aluminum hydroxide (18) with carbonate specifically adsorbed at the edges by unidentate coordination.

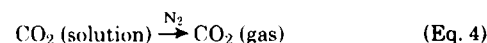
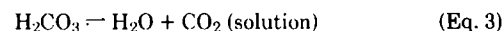
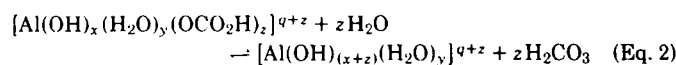
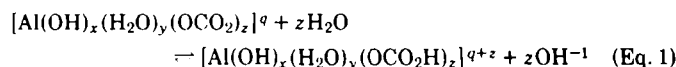
The point of zero charge of both aluminum hydroxycarbonate gels increased during the nitrogen purge (Fig. 3). The increase in the point of zero charge with the desorption of carbonate was expected because gibbsite, the stable polymorph of aluminum hydroxide, has a point of zero charge of 9–10 (4). As seen in Fig. 4, the point of zero charge changes rapidly at very low carbonate/aluminum molar ratios. Therefore, it is not accurate to extrapolate the data in Fig. 4 to zero carbonate content.

The desorption of specifically adsorbed carbonate had a substantial effect on the antacid properties of the aluminum hydroxycarbonate gels as seen in Fig. 5. The presence of a slow-reacting phase was observed within 10–16 d. When virtually all of the carbonate was desorbed, the slow-reacting phase represented nearly all of the sample. Aluminum hydroxycarbonate gels having such a slow rate of acid neutralization will be ineffective as antacids as the rate of acid neutralization is too slow to neutralize any significant quantity of gastric acid during the gastric residence time (19, 20).

The slow-reacting phase was first detected in CG1 on day 16, when the carbonate/aluminum molar ratio was 0.20, and on day 10 in CG2, when the carbonate/aluminum molar ratio was 0.18. This observation suggests that specifically adsorbed carbonate at a minimum carbonate/aluminum molar ratio of 0.20 is necessary to preserve the antacid properties of aluminum hydroxycarbonate gel.

X-ray diffractograms obtained immediately on termination of the nitrogen purging (Fig. 6A and C) were identical to the controls and indicated that CG1 and CG2 were amorphous following carbonate desorption. Thus, X-ray diffraction was insensitive to the structural changes responsible for the loss of acid reactivity as measured by pH-stat titration. This observation emphasizes the value of the pH-stat titration for studying structural changes in antacids. However, X-ray diffraction peaks were observed when the nitrogen-purged samples were allowed to age at room temperature (Fig. 6B and D), indicating that structural changes occur much more readily after specifically adsorbed carbonate has been removed. The position of the X-ray diffraction peak in the aged samples (4.84–4.67 Å in CG1 and 4.82 Å in CG2) suggests that gibbsite, a polymorph of aluminum hydroxide whose most intense X-ray diffraction peak is at 4.82 Å, is the final form of the slow-reacting phase.

The ability of nitrogen gas to remove specifically adsorbed carbonate is believed to be due to a transport mechanism involving a series of interrelated equilibria such as shown below:



Transporting carbon dioxide out of the system with nitrogen caused all of the equilibria to shift to the right, and carbonate was completely desorbed. An increase in pH was observed during carbonate desorption (Fig. 3) which is predicted by Eq. 1. The increase in pH supports a mechanism based on a series of equilibria such as hypothesized above, although any disaggregation which may be caused by the shear force of stirring or nitrogen bubbling may produce a change in pH as the newly exposed surface equilibrates by adsorbing protons in response to the pH-point of zero charge relationship (Fig. 3). The desorption of carbonate by a mechanism based on a series of equilibria as shown above was also proposed as the mechanism responsible for the reduced rate of acid neutralization that was observed following dilution of aluminum hydroxycarbonate gel with water (10). The reversible nature of carbonate adsorption requires that care be taken in the manufacture and packaging of aluminum hydroxycarbonate gel-containing antacids to minimize the desorption of specifically adsorbed carbonate.

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Effect of Coadministration of Uracil on the Toxicity of Tegafur

JYUNJI YAMAMOTO*, AKIHIRO HARUNO*, YUJI YOSHIMURA*, NORIO UNEMI*, YOSHIO KUNIMUNE†, KAZUMASA YAMASHITA‡, and KEN'ICHI MORITA‡

Received September 9, 1982, from the *Department of Pharmacology and †Drug Safety Research Laboratory, Taiho Pharmaceutical Co., Ltd., 224-2 Ebisuno, Hiraishi, Kawauchi-cho, Tokushima 771-01, Japan. Accepted for publication January 10, 1983.

Abstract □ The cardiotoxic and neurotoxic effects of tegafur, an anticancer agent, were compared with those of uracil plus tegafur (4:1 mol/mol) in mice, rats, rabbits, cats and dogs. Uracil plus tegafur was shown to be less toxic than the drug alone in all the species, and uracil was found to decrease the toxicity of tegafur. α -Fluoro- β -alanine, a catabolic metabolite of the drug, had toxic effects similar to tegafur. The results suggest that administration of uracil with tegafur prevents the side effects of the drug on the heart and CNS by inhibiting the degradation of 5-fluorouracil.

Keyphrases □ Tegafur—coadministration with uracil, effect on toxicity, species comparison □ Uracil—coadministration with tegafur, effect on toxicity, species comparison □ Chemotherapeutic agents—coadministration of tegafur and uracil, effect on toxicity, species comparison

Tegafur [5-fluoro-1-(tetrahydro-2-furyl)uracil], synthesized by Hiller *et al.* (1), has been widely used clinically as an anticancer agent because it is a masked form of the pyrimidine antimetabolite, 5-fluorouracil. Jato and co-workers (2, 3) and Mukherjee and Heidelberger (4) reported that the antitumor activity and toxicity of fluorinated pyrimidines are increased by coadministration of pyrimidine. Fujii *et al.* (5-7) found that coadministration of uracil with tegafur increased the 5-fluorouracil level in tumors and the antitumor activity of tegafur, possibly because it inhibits the degradation in the liver of 5-fluorouracil formed from the drug. Moreover, it has been found that uracil plus tegafur (4:1 mol/mol) has stronger antitumor activity than the drug alone, both clinically and in animals (8-12).

Side effects of fluorinated pyrimidines on the heart and CNS have been observed clinically (13-15). But from the

above findings, we suggested previously that uracil might prevent the cardiotoxic and neurotoxic effects of tegafur (16). To test this possibility, we compared the cardiotoxic and neurotoxic effects of the drug alone with those of uracil plus tegafur in mice, rats, rabbits, cats, and dogs.

EXPERIMENTAL

Drugs—The following drugs were used: tegafur¹, 5-fluorouracil², uracil³, and α -fluoro- β -alanine hydrochloride⁴. Tegafur, uracil plus tegafur, and 5-fluorouracil were administered intravenously as their sodium salts and orally as suspensions in 5% gum arabic.

Animals—The following animals were used: male ddY mice (18-23 g)⁵, male Wistar rats (160-200 g)⁵, male Japanese White rabbits (2.5-3.5 kg)⁶, mongrel cats of both sexes (2.3-3.4 kg)⁶, and male Beagle dogs (9.5-10.0 kg)⁷. The animals were used for experiments after a period of acclimatization of at least 7 d in the laboratory at a controlled temperature of 23 ± 1°C and relative humidity of 55 ± 10% with a 12-h light/dark cycle. They were fasted for 18 h before oral administration of drugs.

Methods—Previously, we demonstrated that tegafur at high doses produces clonic convulsions in mice and rats, cardiac fibrillations in rabbits, and vomiting in dogs (16). 5-Fluorouracil has been reported to have a neurotoxic effect in cats (17). These cardiotoxic and neurotoxic effects of tegafur were compared with those of uracil plus the drug in the five species. The acute toxicity of tegafur in these animals was also compared with those of uracil plus tegafur and α -fluoro- β -alanine, a catabolic metabolite of the drug.

Convulsant Effects in Mice and Rats—Groups of 10 mice and rats

¹ Taiho Pharmaceutical Co., Ltd.

² Sigma Chemical Co.

³ Wako Pure Chemical Industries.

⁴ Tokyo Kasei Chemicals.

⁵ Tokushima Laboratory Animals Co.

⁶ Kearly Co.

⁷ Laboratory Research Enterprise, Kalamazoo, Mich.