ness, it is predicted by Eqs. 1 and 2 that the steady-state total flux is proportional to the product of the partition coefficient of the drug between the stratum corneum and the vehicle and its solubility in the vehicle. Although realizing that $K^{M/W}$ was used in the present study rather than $K^{SC/W}$, such a trend nevertheless appears evident since as $K^{M/W} \cdot S_5$ decreases, so does P^{HA} and P^{A^-} (Fig. 2). This suggests the use of this parameter as a relative indicator of permeability when examining a series of analogues for their ability to penetrate human skin, without recourse to actual permeation studies. The data imply that $K^{M/W} \cdot S_5$ must exceed 10–11 mol $\cdot$ L^{-1} before permeation of the chromone-2-carboxylic acids can be detected.

The values of P^{HA} and P^{A^-} obtained from these experiments can be used to determine how the relative permeation rates of the un-ionized and ionized species change with pH and how this affects the total steady-state flux, *i.e.*, $J^{HA} + J^{A^-}$. This is illustrated for I in Fig. 3, where it should be noted that the flux axis is given in log units. As the pH is increased above the pK_a of 1.93, the concentration of the un-ionized species falls. This leads to a continuous reduction in flux due to the un-ionized species, J^{HA}, since the product $P^{HA} \cdot C^{HA}$ is also falling. At the same time, the concentration of the ionized species rises with increasing pH and then remains constant at a pH value 2 or more units above the pK_a. The net effect is a continuous decline in the total flux as the pH of the solution is increased; in the case of I, this increase is to pH 7. Above this pH, the permeation of chromone ions constitutes the major portion of the total flux, although it is important to remember that the magnitude of the total flux falls dramatically as the pH is raised above the pK_a. Thus, for monoprotic acids in which un-ionized and ionized species have widely separated permeability coefficients (*e.g.*, the chromone-2-carboxylic acids in which the difference between P^{HA} and P^{A^-} is $\sim 10^4$), the pH should be held to as low a value as possible when seeking to maximize the total flux through the skin. The optimal value is at least 1 pH unit below the pK_a, assuming satisfactory tolerance by the skin to such a pH. Minimal flux in the example described here occurs at a pH that is ~5 units or more above the pK_a.

Diffusion coefficients (D) for the four compounds are calculated from Eq. 1 by using the values for $K^{M/W}$ given in Table II and a measured stratum corneum thickness of 10 μm. Since P^{HA} is much greater than P^{A^-}, P was taken to be equal to P^{HA}. The values presented in Table II lie within the range normally found for compounds of this size when they are diffused through the stratum corneum (2).

In summary, the results of this study indicate that chromone-2-carboxylic acids permeate human skin both as un-ionized and ionized species, although the former are $\sim 10^4$ times more permeable. Because of the effect of pH on the relative concentrations of un-ionized and ionized species, it would appear to be possible to control the total flux of these compounds by varying the pH of the drug-containing vehicle applied to the skin.

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Adsorption of Phosphate by Aluminum Hydroxycarbonate

JUE-CHEN LIU *§, JOSEPH R. FELDKAMP ‡, JOE L. WHITE ‡, and STANLEY L. HEM *x

Received July 7, 1983, from the **Departments of Industrial and Physical Pharmacy and* ‡*Agronomy, Purdue University, West Lafayette, IN 47907.* Accepted for publication, October 27, 1983. §Present address: College of Pharmacy, Rutgers University, Piscataway, NJ 08854.

Abstract □ Phosphate is specifically adsorbed by aluminum hydroxycarbonate by anion ligand exchange. IR analysis indicated that phosphate exchanged with specifically adsorbed carbonate. Adsorption is favored by low pH and is inversely related to particle size. Adsorption of phosphate decreases the rate of acid neutralization of aluminum hydroxycarbonate. The results are applied to the treatment of hyperphosphatemia and hypophosphatemia.

Keyphrases □ Adsorption—phosphate by aluminum hydroxycarbonate □ Aluminum hydroxycarbonate— adsorption of phosphate

The adsorption of phosphate species by aluminum hydroxide is important, as aluminum hydroxide-containing antacids have been implicated in hypophosphatemia. In contrast, aluminum hydroxide is used as a phosphorus-binding agent in hyperphosphatemia. The interaction of phosphate species with crystalline forms of aluminum hydroxide has been extensively studied due to the wide occurrence of aluminum hydroxide in the soil and the extensive use of phosphorus-containing fertilizers. However, little is known about the interaction of phosphate species with amorphous aluminum hydroxycarbonate, the acid-reactive form of aluminum hydroxide containing specifically adsorbed carbonate which is used in antacids. The purpose of this study was to determine the mechanism of adsorption of phosphate species by aluminum hydroxycarbonate, with emphasis on possible adsorption of phosphate on surface carbonate sites.

BACKGROUND

The binding of phosphorus by aluminum hydroxide in the gastrointestinal tract during antacid therapy was first noted 40 years ago (1, 2). Since that time, it has been confirmed in numerous studies that aluminum hydroxide may reduce the intestinal absorption of phosphate (3–13). Clinical symptoms of phosphorus depletion syndrome parallel serum phosphorus levels and are most likely to be observed in patients who combine aluminum hydroxide antacid therapy with a low dietary phosphorus intake (14, 15). This observation is especially pertinent to critically ill patients who receive only parenteral nutrition and who also require antacid therapy to prevent upper GI bleeding (16).

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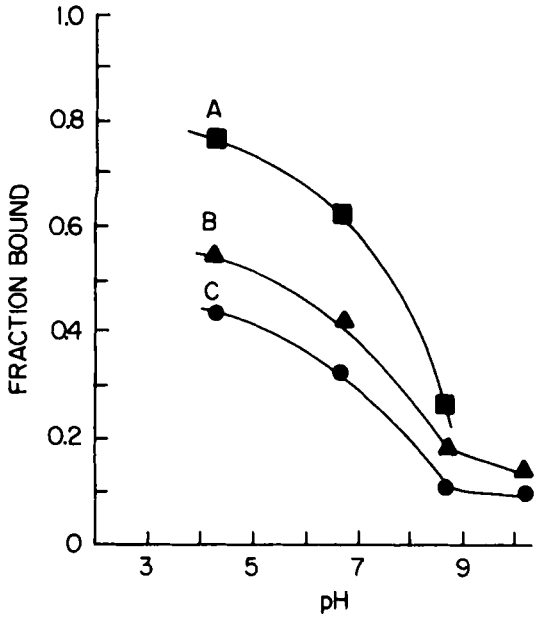


Figure 1—*Effect of pH on the fraction of phosphorus bound by AHCG 1 (A), aluminum hydroxide gel (B), and AHCG 2 (C).*

In two recent studies, slightly different conclusions were reached regarding the effect of aluminum hydroxide on serum phosphorus levels and phosphorus excretion, perhaps due to differences in dosage and duration of therapy. In the first study, seven daily doses containing 525 mg of equivalent aluminum oxide (15.4 mEq) per dose were administered for 28 d to 12 healthy subjects (15). No statistically significant change in serum phosphorus levels occurred, but a statistically significant decrease in phosphorus excretion led to values below the normal phosphorus excretion range. No clinical symptoms were observed in any subject. Because of the change in phosphate excretion, the subjects were described as exhibiting incomplete phosphorus depletion. In a second study, 15 healthy subjects were administered four daily doses containing 450 mg of equivalent aluminum oxide (13.2 mEq) per dose for 12 d (17). Serum phosphorus levels did not change significantly, and no clinical symptoms were observed, although a statistically significant decrease in phosphorus excretion was noted. However, in contrast to the first study, the phosphorus excretion values remained within the normal physiological limits. Therefore, it was concluded that aluminum hydroxide was tolerated by the subjects.

Hyperphosphatemia is most commonly encountered during renal failure. Therapy usually involves reduction in the uptake and absorption of exogenous phosphorus through a low phosphorus diet and the use of phosphorus-binding agents (18–23). Presently, aluminum hydroxycarbonate gel is the chief agent used to treat hyperphosphatemia.

Phosphate species are specifically adsorbed by hydrous metal oxides through anionic ligand exchange, displacing surface hydroxyl or water groups (24).

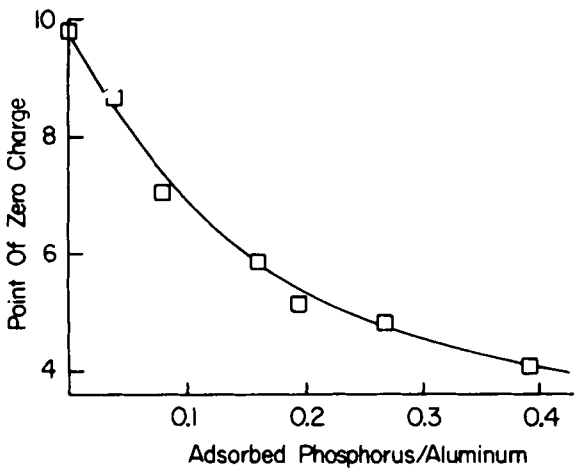


Figure 2—*Effect of phosphate adsorption on PZC of aluminum hydroxide gel.*

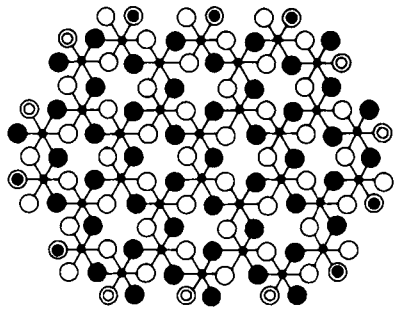


Figure 3—*Schematic of the unit layer of aluminum hydroxide showing the surface hydroxyl and aquo groups. Key: (⊛) upper OH; (○) upper OH_2; (●) lower OH; (⊛) lower OH_2.*

The affinity of anions for aluminum hydroxide at moderate pH conditions follows the order phosphate > arsenate > sulfate > chloride (25). The adsorption of phosphate shifts the point of zero charge (PZC) to lower values and thus alters the surface characteristics (24, 26). This must occur by entering the inner Helmholtz layer, *i.e.*, the first coordination sphere of the aluminum ions on the aluminum hydroxide surface, through the displacement of coordinated hydroxyl and aquo ions by a ligand exchange reaction.

The extent of phosphate adsorption depends on pH, time, concentration, surface area, temperature, and the nature of the adsorbent (26–28).

EXPERIMENTAL SECTION

Materials—Two aluminum hydroxycarbonate gels were obtained commercially and were identified as AHCG 1[1] and AHCG 2[2]. An aluminum hydroxide gel which was free of carbonate was precipitated by adding sufficient 3 M KOH to 2 L of 1 M $AlCl_3$ to reach pH 9.5. Immediately after washing with three volumes of distilled water, 68 g of sorbitol was dissolved in distilled water and added to the aluminum hydroxide gel. The final volume was then adjusted to 4 L by the addition of distilled water. Sorbitol was added to reduce the rate of polymerization (29) and thereby maintain the maximum surface area.

Analytical Procedures—The equivalent aluminum oxide content was determined by chelatometric titration (30). The carbonate content was determined by gasometric displacement (31). The PZC was determined by a potentiometric titration procedure (32). The rate of acid neutralization was determined by automated pH-stat titration[3] at pH 3 and 25°C (33). The amount of phosphorus in solution was determined by the heteropoly blue method (34). The mean hydrodynamic radius was determined by fiber optic Doppler anemometry[4] (35).

The fraction of phosphate species adsorbed at different pH conditions was determined by first adjusting portions of the aluminum hydroxycarbonate or aluminum hydroxide gel containing 15.5 mM of aluminum and 10 mM of KCl to the desired pH with a pH-stat titrator[3]. After the pH adjustment, 25 mL of 1 M NaH_2PO_4 was added, and the volume was adjusted to 100 mL with distilled water. The pH was maintained at the desired level for 1 h at 25°C with constant stirring with the pH-stat titrator[3]. The sample was centrifuged at 15,000 rpm (27,000×*g*) for 30 min, and the supernatant was analyzed for phosphorus. The quantity of phosphate adsorbed was determined by difference.

IR spectra[5] were obtained by air drying the sample and preparing a com-

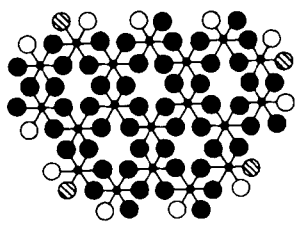


Figure 4—*Schematic of the unit layer of aluminum hydroxycarbonate showing the surface hydroxyl, aquo, and carbonate groups. Key: (●) OH; (○) OH_2; (⊘) CO_3.*

[1] Chattem Chemical Co., Chattanooga, Tenn.
[2] Reheis Chemical Co., Phoenix, Ariz.
[3] PAM 62, TTT 60, ABU 12, TTA 60, REA 160; Radiometer, Copenhagen, Denmark.
[4] SIRA Institute, Ltd., Kent, England.
[5] Model 180; Perkin-Elmer Corp., Norwalk, Conn.

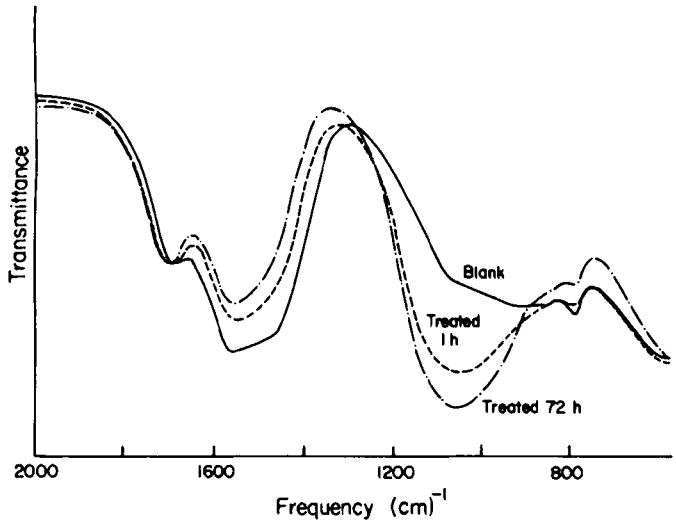


Figure 5—*Change in the IR spectrum of AHCG 2 as a result of phosphate adsorption. Key: (—) blank; (- -) treated for 1 h; (— • —), treated for 72 h.*

pressed disk (1 mg of sample/300 mg of KBr). A sample of AHCG 2 containing 25 mM of equivalent aluminum oxide was diluted to 100 mL with distilled water and adjusted to pH 6.6. Five milliliters of 0.25 M NaH_2PO_4 was added. The sample was shaken at 25°C. Portions were removed and air dried after 1 and 72 h.

The exchange of phosphate species for specifically adsorbed carbonate in aluminum hydroxycarbonate was determined by adding 26.9 mM NaH_2PO_4 to a sample of AHCG 2 containing 15.5 mM equivalent aluminum oxide at pH 6.6 and 25°C. The pH was maintained with a pH-stat titrator[3]. Samples were taken after 30, 60, 120, or 240 min of reaction time and analyzed for total carbonate content and phosphorus in solution.

RESULTS AND DISCUSSION

Phosphate is adsorbed by both aluminum hydroxide and aluminum hydroxycarbonate (Fig. 1). The three adsorbents differed substantially in the amount of phosphate adsorbed. However, this difference does not appear to be related to the presence of carbonate surface groups, in addition to hydroxyl and aquo surface groups, as the fraction of phosphate bound by the sample of aluminum hydroxide (Fig. 1B) was intermediate between the two aluminum hydroxycarbonate gels (Fig. 1A and C). Particle size analysis showed that phosphate adsorption was directly related to surface area, as the mean hydrodynamic radii of aluminum hydroxycarbonate gel 1 (AHCG 1), aluminum hydroxide, and aluminum hydroxycarbonate gel 2 (AHCG 2) were 0.21, 0.28, and 0.51 μm, respectively.

The results shown in Fig. 1 also indicate that phosphate adsorption is dependent on pH, with all three adsorbents exhibiting a similar pH profile. However, the PZC varies from 9.8 for aluminum hydroxide to 7.6 and 6.5 for aluminum hydroxycarbonate 1 and 2, respectively. Thus, phosphate adsorption cannot be explained simply by electrostatic attraction, as the pH profile is not related to the PZC of the adsorbents. The fact that phosphate adsorption is independent of the PZC, *i.e.*, adsorption decreased at pH ~7 for all three adsorbents, indicates that phosphate is specifically adsorbed at the inner Helmholtz layer by a ligand-exchange reaction (24) which is independent of surface potential.

The nature of the surface and the ionic form of the adsorbate are influenced by pH. At low pH conditions, the surface is positive and aquo groups are the predominant sites on the surface. As the pH increases, the surface potential decreases and more hydroxyl sites occur on the surface as the hydroxide concentration in solution increases. Therefore, the phosphate species must compete with hydroxide ions for the hydroxyl sites on the increasingly negative surface. Thus, the high adsorption of phosphate species at low pH can be attributed to the high positive charge of the surface and the weaker competition of hydroxide ions. This behavior is in agreement with the results of a previous study by Huang (27), who concluded that surface acidity and the acid–base behavior of the adsorbed anions are the most important factors controlling the adsorption density.

The conclusion that phosphate is specifically adsorbed by aluminum hydroxide and aluminum hydroxycarbonate is further supported by the depression of the PZC of aluminum hydroxide following phosphate adsorption (Fig. 2). The PZC decreased from 9.8 to 4.1 as the adsorbed phosphate-to-aluminum molar ratio increased from 0 to 0.39. The decrease in PZC can be attributed to the negative charge introduced by the specifically adsorbed phosphate (27).

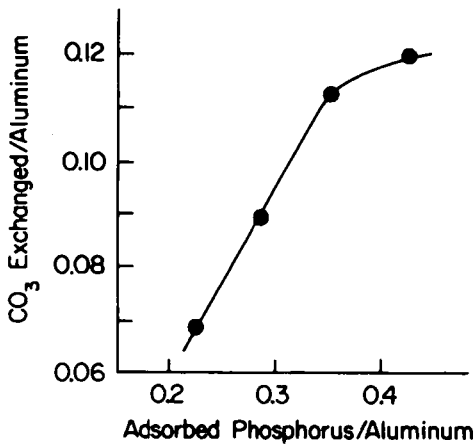
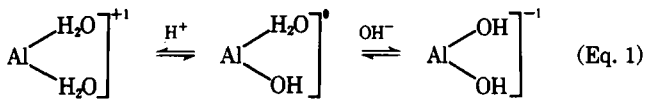


Figure 6—*Exchange of phosphate species for specifically adsorbed carbonate in AHCG 2 at pH 6.6 and 25°C.*

The potential exchangeable sites for aluminum hydroxide are illustrated in Fig. 3. The molecular structure is composed of two fundamental units: two planes of closely packed hydroxyl ions with aluminum sandwiched between them as fused, six-membered rings of octahedrally coordinated aluminum atoms joined by double hydroxide bridges (36). At the surface, the terminal aluminum atoms are coordinated with hydroxyl and aquo groups. The proportion of hydroxyl and aquo surface groups is controlled by the pH–PZC relationship (37) by[6]:



(Eq. 1)

Rajan *et al.* (38) have shown that aquo groups are the predominant adsorption site at low pH conditions and that exchange with surface hydroxyl groups predominates above pH 6.7.

Aluminum hydroxycarbonate has the same basic structure as aluminum hydroxide, except that carbonate groups are present at the surface in addition

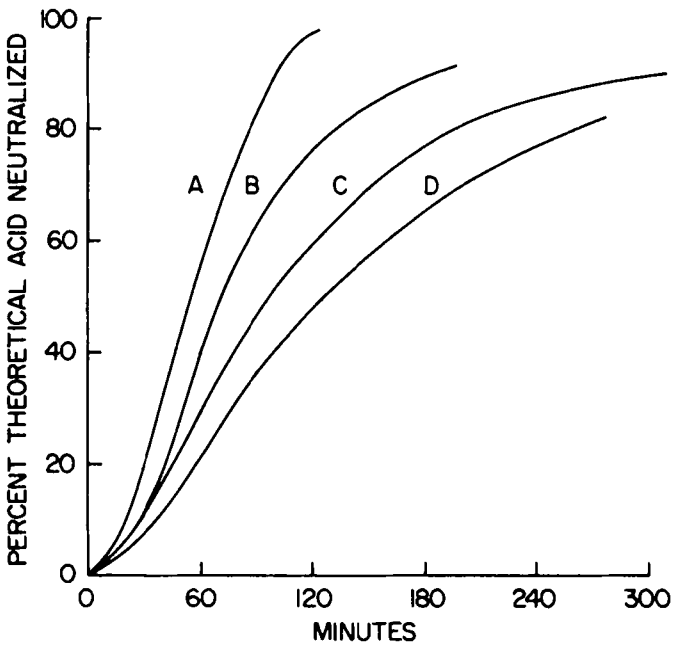


Figure 7—*Effect of phosphate adsorption on the rate of acid neutralization of AHCG 2 at various adsorbed phosphate-to-aluminum molar ratios. Key: (A) 0; (B) 0.016; (C) 0.032; (D) 0.066.*

[6] For clarity, only the bonds associated with the surface sites are shown, even though aluminum is in sixfold coordination in each structure.

to hydroxyl and aquo groups (39) (Fig. 4). The possibility of exchange of phosphate for surface carbonate sites was studied by IR spectroscopy (Fig. 5). The IR spectrum of aluminum hydroxycarbonate exhibits absorption bands between 1400 and 1500 cm^{-1} which have been assigned to specifically adsorbed carbonate (40). After interacting with phosphate for 1 h, the carbonate bands were diminished, and a band at 1080 cm^{-1}, corresponding to P—O stretching (41), was evident. The P—O stretching band increased in intensity with adsorption time while a concomitant decrease in the intensity of the carbonate band occurred. The exchange of phosphate species for carbonate was confirmed by the loss of carbonate which accompanied adsorption of phosphate by AHCG 2 at pH 6.6 (Fig. 6). At low phosphate levels, the ratio of phosphate adsorbed to carbonate exchanged was ~3, indicating that phosphate adsorption by aluminum hydroxycarbonate gel involves exchange with surface carbonate sites as well as hydroxyl and aquo sites.

The effect of phosphate adsorption on the rate of acid neutralization of aluminum hydroxycarbonate was investigated by pH-stat titration at pH 3 and 25°C (Fig. 7). The rate of acid neutralization decreased in response to adsorption of even small amounts of phosphate. For example, the time to neutralize 50% of the sample increased from 57 min, in the absence of phosphate, to 75 min when the adsorbed phosphate-to-aluminum molar ratio was only 0.016. The mechanism for this effect is believed to be related to the difference in solubility between $AlPO_4$, known mineralogically as berlinite, and amorphous aluminum hydroxide. The acid neutralization reactions of $AlPO_4$ and $Al(OH)_3$ are shown by:

$$AlPO_4 + 3H^+ \overset{K_1}{\rightleftharpoons} Al^{3+} + H_3PO_4 \qquad \text{(Eq. 2)}$$

$$Al(OH)_3 + 3H^+ \overset{K_2}{\rightleftharpoons} Al^{3+} + 3H_2O \qquad \text{(Eq. 3)}$$

The logarithims of the equilibrium constants for Eqs. 2 and 3 are 0.5 and 9.66, respectivcly (42). Thus, the Al—O—PO_3 bond is much more resistant to proton attack than the Al—O—H bond.

Adsorption of phosphate species occurs as readily by aluminum hydroxycarbonate as by aluminum hydroxide because phosphate can exchange with specifically adsorbed carbonate. Adsorption is favored by low pH and small particle size. In patients with hypophosphatemia, the depletion of phosphorus will be the greatest for those aluminum hydroxycarbonate gels with the smallest particle size, *i.e.*, those exhibiting the best antacid properties. Thus, an adequate dietary intake of phosphorus is essential of antacid therapy is required. Alternate steps, such as the use of aluminum phosphate gel as an antacid, are not satisfactory because of the poor antacid properties of aluminum phosphate. On the other hand, an aluminum hydroxide gel with the maximum surface area appears to be desirable to treat hyperphosphatemia. The aluminum hydroxide gel used in this study, which was stabilized by adding sorbitol immediately after precipitation (Fig. 1B), would be a good candidate, as it requires 270 min to neutralize 10% of its theoretical acid-neutralizing capacity at pH 3 and 25°C. Thus, this aluminum hydroxide gel will not undergo appreciable acid dissolution during the gastric residence time and will be present throughout the GI tract as a relatively high-surface-area colloidal solid capable of adsorbing phosphate species.

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