only 581.9 µg of digoxin was removed. Seventy-five minutes was required postperfusion before the system reached 90% of equilibration.

In Fig. 1C, Q_s was slowed by a factor of 10. Digoxin levels in V_c and V_f fell rapidly to 1.6 ng/ml, and hemoperfusion in this setting apparently was very effective. However, digoxin levels in V_s fell very slowly, and only 204.8 µg of digoxin was removed. Reequilibration was 90% complete in 705 min.

DISCUSSION

As can be seen in Table I, the amount of digoxin in V_s continued to fall after the completion of perfusion as V_c and V_f were refilled. If the pharmacological effect of digoxin or any other drug takes place in V_s then the adverse effect of those drugs with rapid intercompartment clearances can be rapidly decreased by hemodialysis or hemoperfusion. As Q_s decreases, changes in concentration in V_c will become greater with dialysis or hemoperfusion, but there will be little net reduction in pharmacological effects or total body burden with short perfusion times. However, if the pharmacological effect is in V_c, the toxicity of drugs with slow intercompartment clearances will be rapidly reversed, only to return as this compartment is refilled from V_s.

Schreiner (3) correctly pointed out that the effectiveness of the arti-ficial kidney in removing substances will depend upon the rapid equilibration of the substance with plasma water. However, some nephrologists neglect this fact and feel that V_d per se is the rate-limiting factor controlling the effectiveness of drug removal. Clearly, while a large V_d influences the effectiveness of dialysis or hemoperfusion, the rate-limiting step may be the rate of movement of drug from V_s to V_c.

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Factors Affecting Homogeneous Precipitation of Aluminum Hydroxide Gel

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Abstract □ The variables affecting homogeneous precipitation in the hydrolysis of aluminum nitrate by sodium carbonate were studied. Increased temperature, decreased concentration of reactants, and decreased rate of addition of titrant favor conditions that achieve homogeneous precipitation. During acid hydrolysis, the nitrate anion was the major anion associated with the gel and only small amounts of carbonate were observed. It is recommended that homogeneous conditions be achieved during the precipitation of aluminum hydroxide gel to improve reproducibility.

Keyphrases □ Aluminum hydroxide gel—factors affecting homogeneous precipitation in hydrolysis of aluminum nitrate by sodium carbonate □ Antacids—aluminum hydroxide gel, factors affecting homogeneous precipitation in hydrolysis of aluminum nitrate by sodium carbonate

The precipitation of aluminum hydroxide gel through the hydrolysis of an aluminum salt is complex. The precipitation method and subsequent treatment have a great effect on the properties of the product (1–4). This variability has been a problem affecting all areas of research and production of aluminum hydroxide gel.

In the titration of aluminum nitrate with sodium hydroxide, polymerization occurs prior to precipitation under homogeneous conditions (5, 6). This was achieved by precipitation under carefully controlled conditions in a specially designed reaction chamber. Precipitation of aluminum hydroxide gel under homogeneous conditions may be important in reducing the variability in precipitation.

Studies were undertaken to determine if homogeneous precipitation conditions could be achieved using standard precipitation equipment. The effect of precipitation variables was then investigated to determine the contribution of each variable in the achievement of a homogeneous reaction.

The system studied was the precipitation of aluminum hydroxide from acidic media (5, 6). However, sodium carbonate was used as the titrant instead of sodium hydroxide because the aluminum hydroxide gels used as antacids usually contain carbonate (7, 8).

EXPERIMENTAL

Potentiometric titrations were performed by placing 100 ml of solution in a 400-ml jacketed beaker. The temperature was controlled to ±0.1°, and the solution was stirred[2] at 2000 rpm. Titrant was added at a controlled rate[3]; the standard rate of addition was 2 ml/min. The solution pH was monitored continuously and recorded. Exact replication of titration curves was obtained when conditions producing homogeneous precipitation were used.

IR analysis[4] (9) was performed on a portion of the aluminum hydroxide, which was washed with three volumes of water to remove excess salts prior to drying under vacuum at room temperature. Spectra were obtained using potassium bromide pellets.
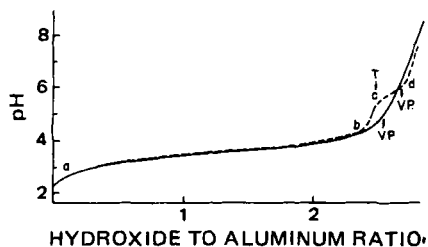
RESULTS AND DISCUSSION

Titration of 0.5 M aluminum nitrate by 0.5 N NaOH at 22° (Fig. 1)

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[2] Stedi-Speed stirrer, Fisher Scientific, Pittsburgh, Pa.
[3] Solution metering pump, model 746, Beckman Instruments, Fullerton, Calif.
[4] Model 180, Perkin-Elmer Corp., Norwalk, Conn.

Figure 1—*Effect of temperature on the titration of 0.5 M aluminum nitrate with 0.5 N NaOH at an addition rate of 2 ml/min. Key: —, 22°; ---, 40°; T, turbidity; and VP, visible precipitate.*

resulted in a continuous curve similar to those commonly reported (10). Under these conditions, polymerization and precipitation were not separate processes but occurred simultaneously.

At 40°, a different titration curve, which exhibited two plateaus characteristic of homogeneous precipitation (5, 6), was obtained. Turbidity associated with polymerization of the hydroxyaluminum units occurred at the beginning of the second plateau (hydroxide to aluminum ratio = 2.46). A visible precipitate, indicating the initiation of the precipitation phase, first appeared at the end of this plateau (hydroxide to aluminum ratio = 2.70). In contrast, under nonhomogeneous conditions, turbidity and the formation of a visible precipitate appeared simultaneously at a hydroxide to aluminum ratio of 2.50. Precipitation occurs over a more restricted hydroxide to aluminum ratio and pH under homogeneous conditions and should produce a more uniform product.

The relatively constant pH observed from a to b in Fig. 1 indicates that a strong binding of hydroxides by aluminum is occurring. The reaction during this plateau can be written as shown in Scheme I:

$$XAl^{3+} + YOH^- \rightarrow Al_X(OH)_Y{}^{3X-Y}$$

Scheme I
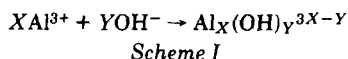
This part of the titration does not appear to be affected by precipitation conditions because of the small size of the ionic species formed during this plateau. The hydroxide to aluminum ratio of 2.33 (point b) indicates an average polymeric species consisting of four fused six-member rings with the formula $Al_{16}(OH)_{38}^{10+}$ (10). The titrations now behave differently as polymerization of these primary units occurs under homogeneous conditions, but polymerization and precipitation both proceed simultaneously under nonhomogeneous conditions. Under homogeneous conditions, further addition of sodium hydroxide (b to c) produces a sharp increase in pH, but the solution remains clear. The added hydroxides are neutralizing protons rather than combining with hydroxyaluminum polymeric units.

Turbidity is observed at the beginning of the second plateau (point c). The added hydroxides are adsorbed by the hydroxyaluminum polymers during this plateau. The charge is reduced, and the polymerization of several units occurs. Polymerization increases until the charge on the polymer sheets is reduced enough to permit aggregation, which leads to the formation of a visible precipitate (point d). The pH increases sharply since the added hydroxides are not completely incorporated into the solid phase.

Thus, the polymerization and precipitation phases in the preparation of aluminum hydroxide can be separated using standard laboratory equipment.

In the aluminum nitrate–sodium carbonate system, which is of greater importance for antacids, the effects of temperature, concentration of reactants, and rate of addition of titrant were determined by carefully
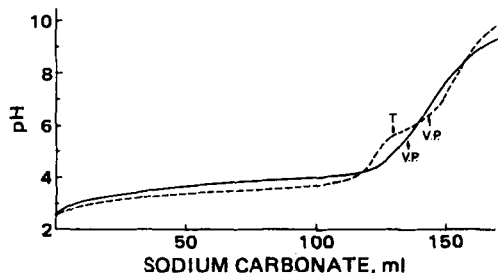
Figure 2—*Effect of temperature on the titration of 0.5 M aluminum nitrate with 0.5 M sodium carbonate at an addition rate of 2 ml/min. Key: —, 23°; ---, 46°; T, turbidity; and VP, visible precipitate.*
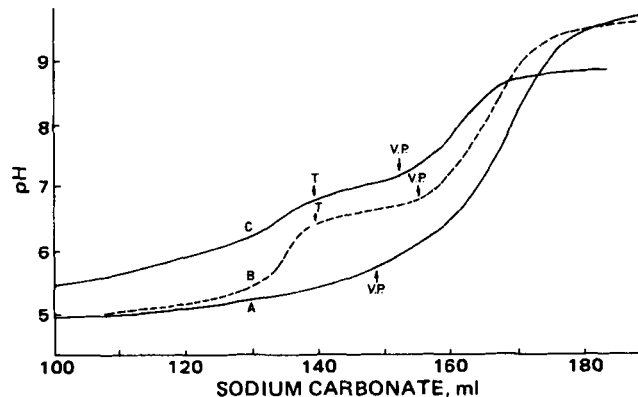

Figure 3—*Effect of concentration and addition rate on the titration of aluminum nitrate with sodium carbonate at 22°. Key: A, 0.1 M aluminum nitrate with 0.1 M sodium carbonate, 5 ml/min; B, 0.1 M aluminum nitrate with 0.1 M sodium carbonate, 2 ml/min; C, 0.005 M aluminum nitrate with 0.005 M sodium carbonate, 5 ml/min; T, turbidity, and VP, visible precipitate.*

varying one factor at a time. The effect of temperature is observed in Fig. 2. The titration curve assumed the characteristics of a homogeneous precipitation as the temperature was increased from 23 to 46°. This result indicates that the increased diffusion rate produces more uniform conditions throughout the reaction medium. Similarly, a decrease in the concentration of the reactants or in the titrant addition rate produced conditions resulting in homogeneous precipitation (Fig. 3).

The important characteristic of a system exhibiting homogeneous precipitation is that every volume of reactant is equally exposed to the titrant, resulting in a controlled process whereby polymerization precedes precipitation. Precipitation conditions should be chosen to achieve homogeneous conditions. However, elevated temperatures are not recommended to produce homogeneous conditions because numerous reports indicated that high temperatures have a deleterious effect on the antacid properties of aluminum hydroxide gel (11, 12).

Comparison of the titration curves utilizing sodium hydroxide or sodium carbonate (Figs. 1 and 2) indicates that a similar reaction occurs in both systems, suggesting that carbonate does not play an important role in the precipitation of aluminum hydroxide from acidic media. Analysis of the precipitate by IR spectroscopy showed that nitrate was the major anion associated with the gel up to pH 8.0, although a small amount of carbonate was also observed. Above this pH, nitrate progressively disappeared, presumably replaced by hydroxides. This result is seen in Fig. 4 where the absorption band at 1382 cm⁻¹ is due to nitrate, the bands at 1400 and 1535 cm⁻¹ are due to carbonate, and the band at 1635 cm⁻¹ is due to water.

Precipitation under homogeneous conditions appears to produce a
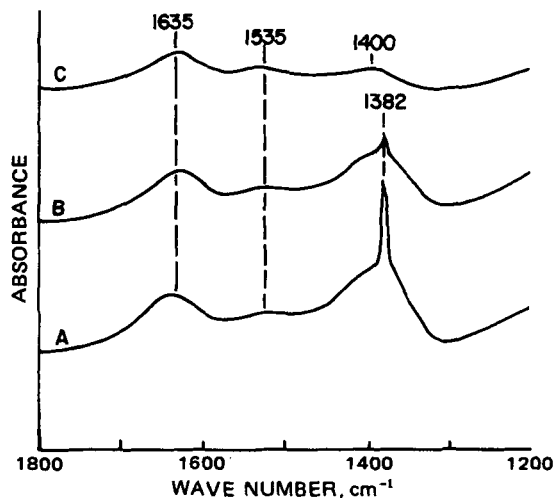
Figure 4—*IR spectra of precipitates at different pH values during titration of 0.1 M aluminum nitrate with 0.1 M sodium carbonate at an addition rate of 2 ml/min at 22°. Key: A, pH 8; B, pH 9; and C, pH 10.*

more consistent product in terms of particle size and charge. Since these properties have important effects on acid reactivity and viscosity, the achievement of homogeneous conditions during precipitation should reduce the variability in the properties of aluminum hydroxide gel. It is recommended that the precipitation system be checked to determine if homogeneous conditions exist by performing an acid titration and determining if polymerization occurs separately from precipitation.

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Omission of Pepsin from Simulated Gastric Fluid in Evaluating Activated Charcoals as Antidotes

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Abstract ☐ Although simulated gastric fluid USP calls for 3.2 g of pepsin/liter, most researchers omit pepsin when evaluating adsorbents. The present results show that, although pepsin adsorbs strongly to activated charcoal, it does not interfere significantly with the adsorption of a typical drug like sodium salicylate. Therefore, its omission is justified. Gastric mucin also had almost no effect on salicylate adsorption.

Keyphrases ☐ Pepsin—effect on adsorption of typical drugs to activated charcoal *in vitro* ☐ Charcoal, activated—adsorption of typical drugs, effect of pepsin *in vitro* ☐ Adsorption, *in vitro*—typical drugs to activated charcoal, effect of pepsin ☐ Gastric fluid, simulated—*in vitro* adsorption of typical drugs to activated charcoal, effect of pepsin

typical test substance. The omission of gastric mucin is also discussed.

An adsorbent like activated charcoal can be evaluated as a potential orally administered poison antidote by dissolving a test substance in simulated gastric fluid, adding the adsorbent, and measuring the amount of drug adsorbed after equilibrium is achieved.

Although simulated gastric fluid USP contains, per liter, 3.2 g of pepsin, 2.0 g of sodium chloride, and 7.0 ml of hydrochloric acid USP (giving a pH of 1.2), it is common practice to omit the pepsin and sodium chloride in preparing simulated gastric fluids. While sodium chloride does not adsorb to materials like activated charcoal, activated charcoal strongly inactivates (1) and strongly adsorbs (2) pepsin. The possibility arises that pepsin would compete with the test substance for available adsorption sites, so its omission from simulated gastric fluid could result in a falsely high value for the amount of drug bound by the adsorbent under actual gastric conditions.

The purpose of this study was to investigate whether the inclusion or omission of pepsin from simulated gastric fluid significantly affects the measured degree of binding of a

BACKGROUND

The adsorbing ability of substances like activated charcoal has been assessed by dissolving the test drug in distilled water (3, 4). Since pH has a very strong influence on drug adsorption capacities (5–7), the results are not necessarily relevant to what would occur *in vivo.* For this reason, dilute hydrochloric acid solutions (usually 0.1 M, pH 1.0) often are used (8–13) as simulated gastric fluid. Such solutions are different from simulated gastric fluid USP in that they do not contain pepsin. Some investigators (11–13) specifically mentioned the deliberate omission of pepsin but did not comment on any possible effect. Apparently, any dilute hydrochloric acid solution of pH 1–2 is considered a valid and equivalent substitute for simulated gastric fluid USP, if not for actual gastric fluid itself.

Piper and Fenton (1) showed substantial inactivation of pepsin dissolved in a pH 1.5 potassium chloride–hydrochloric acid buffer by various adsorbents (charcoal, aluminum hydroxide, and clays). This inactivation was most likely the result of the pepsin having been adsorbed; however, direct evidence of such adsorption was not presented. Lichtwitz and Greef (2) published direct evidence of a substantial adsorption of pepsin onto various similar adsorbents. Thus, pepsin can bind well to several common adsorbents (and rather strongly to activated charcoal in particular).

Based on a molecular weight of pepsin of about 35,000, its equivalent spherical molecular radius is about 20 Å. This radius would allow pepsin to penetrate all macropores (>1000 Å) and a substantial fraction of the micropores in many adsorbent materials. For example, in most typical activated charcoals, about 50–90% of the pore volume resides in the pores of radii greater than 20 Å. Any test drug (*e.g.,* aspirin) would be much smaller in molecular size and could reach the smaller pores (<20 Å radius) where a substantial amount of the internal surface area resides. (Even if the pores of 20 Å radius or less are only 10% of the total pore volume, they would contribute a much larger proportion of the total internal surface area.)

Therefore, pepsin and a typical drug might compete strongly in the