

THE PREPARATION AND *IN VITRO* EVALUATION OF SOME MODIFIED ALUMINIUM HYDROXIDES AS GASTRIC ANTACIDS

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The preparation and properties of some aluminium hydroxides modified by carbohydrates are described. *In vitro* evaluation of their antacid properties shows that they are quick acting products of high neutralising capacity and capable of prolonged buffering in the pH range 3 to 4. They compare well in a variety of tests with liquid aluminium hydroxide gel.

LIQUID aluminium hydroxide gel has antacid activity which is both rapid and protracted in the desirable pH range 3 to 4. The dried gel on the other hand is slow in its antacid action, its activity is greatly diminished in the presence of pepsin and peptone, and further, there is a reduction in its rate of reaction with acids upon ageing.

The conditions used in preparation of the aluminium hydroxide influence the type of product formed (Lewis and Taylor, 1958); i.e. whether it is hydragillite, bayerite, boehmite or amorphous. When amorphous aluminium hydroxides prepared from aqueous solutions are dried to a critical water content, there is a rapid decrease in surface area upon storage (Harris and Sing, 1957). Such ageing does not occur in the dry state, but is dependent upon the presence of water vapour (Harris and Sing, 1957). However, aluminium hydroxides prepared from aluminium isopropoxide are much more resistant to ageing. The final surface area does not fall below 300 m.²/g., whereas those from aqueous solutions fall to about 60 m.²/g. (Harris and Sing, 1958). In addition, the low temperature nitrogen adsorption isotherms on products prepared from aluminium isopropoxide differ from those obtained on products from aqueous systems. The latter give a typical reversible S type curve indicating that there is no well defined pore structure, whilst those prepared from aluminium isopropoxide are more complicated, showing pronounced hysteresis loops characteristic of adsorption on a porous solid and resembling those obtained on "activated" alumina (Harris and Sing, 1960). It occurred to us that this type of aluminium hydroxide might be superior to dried aluminium hydroxide gel in antacid activity and in rapidity of action, and that it would not deteriorate so markedly upon storage. The use of carbohydrates as additives in the preparation of such products has been examined.

EXPERIMENTAL

Preparation of Products

Aluminium isopropoxide was freshly distilled before use.

Aluminium hydroxide. A solution of aluminium isopropoxide in an equal weight of xylene was heated under reflux with stirring and the theoretical quantity of water to convert the isopropoxide to hydroxide

was added dropwise over 1 hr. The precipitate was matured in the refluxing solution for a further 30 min., filtered off, washed with xylene and dried at 50°.

Aluminium hydroxide modified with carbohydrates. Aluminium isopropoxide (redistilled: 51 g., 102 g., or 204 g., depending on the additive-water ratio to be added) was added to isopropanol and the whole heated to reflux in an oil bath. The mixed reactants (additive and water) were then mixed with a further volume of isopropanol. The total isopropanol used to dilute the aluminium isopropoxide and reactants was always 400 ml. The mixed reactants were then added dropwise, with

TABLE I
MODIFIED ALUMINIUM HYDROXIDES

Additives	No. moles per mole aluminium isopropoxide	Weight g. aluminium isopropoxide	Weight additive g.	Weight H ₂ O g.	Yield g.
None	—	102	—	21	37
Sucrose	1/3	51	28.5	9	42
	1/6	51	14.25	9.75	31
	1/12	51	7.1	10.1	24
	1/24	102	7.1	20.6	42
	1/48	102	3.55	20.85	38
	1/96	102	1.77	20.95	36
Glucose	1/3	102	30	18.0	63
	1/6	102	15	19.5	52
	1/12	102	7.5	20.2	44
	1/24	102	3.8	20.6	42
Sorbitol	1/3	204	60.7	36	122
	1/6	204	30.3	39	92
	1/12	204	15.17	40.5	80
	1/24	204	7.6	41.2	80

stirring, to the aluminium isopropoxide over about 30 min.; the reaction mixture was heated a further 30 min. and, after cooling a little, the product was filtered off and air dried at 50° to constant weight.

With the higher additive-water ratios, where the amount of water was inadequate to dissolve the carbohydrate, the reactants were added in a slurry with isopropanol. All products were white powders. The glucose compounds, which were yellow when filtered off, dried to off-white powders. A modified aluminium hydroxide without carbohydrate, using water only as reactant, was also prepared.

A list of the modified aluminium hydroxides is given in Table I.

Evaluation of Products

Neutralising capacity. This was determined by the method of the British Pharmacopoeia 1958 for dried aluminium hydroxide gel.

Rapidity of action. A sample of the antacid (0.5 g.) was added, with stirring, to 50 ml. of 0.1N hydrochloric acid at 37°, and the pH values recorded after specific time intervals. Two or more determinations were made with each antacid.

Buffering capacity. A slurry of the compound under test was prepared by adding the finely powdered solid (1.0 g.) to distilled water (200 ml.).

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The whole was maintained at 37° and stirred at a constant speed throughout the test. N Hydrochloric acid (1 ml.) was added and when the system had equilibrated the pH was recorded. Further 1 ml. quantities were added, and the pH recorded after each addition. The buffering capacity is defined as the number of ml. of N hydrochloric acid required to change the pH from 4 to 3, and was determined graphically.

Buffering action given by repeated doses. Three successive 0.5 g. samples were added at 15 min. intervals to 0.1N hydrochloric acid (50 ml.) at 37°. The pH values were recorded every 5 min., two or more determinations being made with each antacid.

TABLE II

THE EFFECT OF ADDITIVE UPON THE BUFFERING AND NEUTRALISING CAPACITY DETERMINED BY THE METHOD IN THE B.P. 1958 FOR DRIED ALUMINIUM HYDROXIDE GEL

Type of $Al(OH)_3$	pH after			Ml. 0.1N NaOH	Neutralising capacity ml. 0.1N HCl
	10 min.	15 min.	20 min.		
$Al(OH)_3$ ex xylene	1.54	1.57	1.59	99	102
Modified $Al(OH)_3$ — No additive	1.9	2.4	3.5	24.2	251.6
Modified $Al(OH)_3$ — Sucrose	1.85	1.86	1.87	71.3	157.4
1/3M	3.03	3.22	3.30	46.0	208.0
1/12	3.42	3.50	3.53	28.0	244.0
1/24	3.60	3.70	3.70	10.0	280.0
1/48	3.35	3.55	3.60	14.7	270.6
1/96	3.61	3.65	3.68	2.1	295.8
Modified $Al(OH)_3$ — Glucose	3.3	3.4	3.4	42.2	215.6
1/3M	3.5	3.6	3.6	22.6	254.8
1/12	3.4	3.6	3.65	13.2	273.6
1/24	3.6	3.6	3.68	3.5	293.0
Modified $Al(OH)_3$ — Sorbitol	2.6	3.2	3.5	38.9	222.2
1/3M	2.7	3.5	3.65	30	240
1/12	3.3	3.55	3.7	22.3	255.4
1/24	3.6	3.7	3.72	5.2	289.6
Dried Aluminium Hydroxide Gel B.P.	1.8	2.5	3.3	20.1	260

Buffering action in artificial gastric medium. The artificial gastric medium used was that of Brindle (1953) and consisted of 0.05N hydrochloric acid buffered with 0.15 per cent of pepsin, 0.15 per cent of peptone and 0.15 per cent of sodium chloride. The test method required the measurement at regular intervals of the pH of the artificial gastric juice at 37° from the time of adding the antacid (0.5 g.) until all the antacid had been consumed. Initially 150 ml. of artificial gastric juice was used, this had pH 1.45; 2 ml. of fresh juice were added every min. and after each 10 min. interval, 20 ml. of the total artificial gastric mixture were withdrawn and rejected.

Measurement of the specific surface area. The specific surface areas of the powders were determined by the air permeability method based on the resistance to the flow of air by a bed of powder packed under standardised conditions. The apparatus was that described by Rigden (1943) and Hughes (1959).

RESULTS AND DISCUSSION

It is clear from the results that aluminium hydroxide precipitated from aluminium isopropoxide without additives offers no advantages over dried aluminium hydroxide gel B.P. as an antacid and that some modification of the composition is necessary if an improved antacid is to be

TABLE III
THE EFFECT OF ADDITIVE UPON THE BUFFERING CAPACITY, THE NEUTRALISING CAPACITY, THE SPECIFIC GRAVITY AND THE SPECIFIC SURFACE AREA

Type of Al(OH) ₃	Buffering capacity ml. N HCl/g.	Neutralising capacity ml. 0.1N HCl/g.	Specific gravity	Surface area m. ² /g.
Al(OH) ₃ ex xylene	7.1	102	2.1	6.2
Modified Al(OH) ₃ -- No additive	13.6	251.6	2.0	12.0
Sucrose 1/3M	10.5	157.4	2.0	6.7
1/6	12.1	208.0	1.9	5.1
1/12	16.6	244.0	1.8	8.4
1/2	19.4	280.0	1.8	11.0
1/48	19.0	270.6	1.77	11.5
1/96	18.8	295.8	2.0	12.7
Glucose 1/3M	—	215	—	—
1/6	16	254	1.8	9.6
1/12	—	273	—	—
1/24	—	293	—	—
Sorbitol 1/3M	17	222.2	—	—
1/6	15	240.0	1.6	8.2
1/12	16	255.4	—	—
1/24	21	289.6	—	—
Dried Aluminium Hydroxide Gel B.P. ..	16.4	260	1.9	10.2

made from aluminium isopropoxide. The use of glucose and sucrose to suppress bayerite formation in aluminium hydroxides precipitated by the decomposition of sodium aluminate solution (Sato, 1960), made the use of such substances as modifying agents an obvious first choice. Additionally, not only do carbohydrates possess hydroxyl groups which can

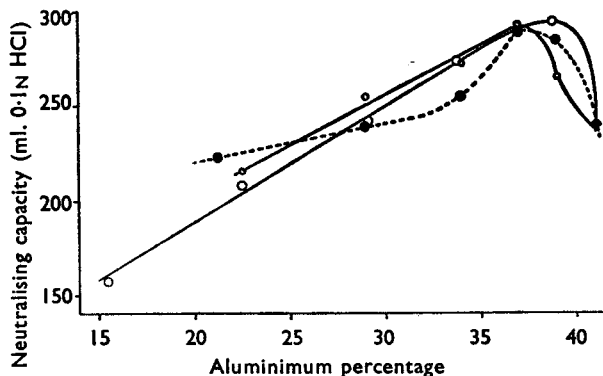


FIG. 1. The relation between neutralising capacity and aluminium percentage
—○—○— = sucrose modified; —○—○— = glucose modified; --●---●--
= sorbitol modified.

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replace the isopropoxy groups attached to aluminium in aluminium isopropoxide, but also they are non-toxic and can be assimilated by the body.

An ideal antacid should possess several properties; (i) it should be quick in its initial effect; (ii) the effect should be such that the pH of the gastric juices is not raised high enough to inhibit pepsin activity or to bring about acid rebound; (iii) it should have a high neutralising capacity and should maintain this effect over a prolonged period; (iv) it should be non-irritating to and should not be adsorbed by the alimentary tract; (v) it should not effervesce and cause flatulence, and (vi) it should be palatable.

A plot of the neutralising capacity (Table II) against aluminium percentage for each additive is given in Fig. 1. In every instance a curve is obtained with a maximum, showing that while a minimum amount of

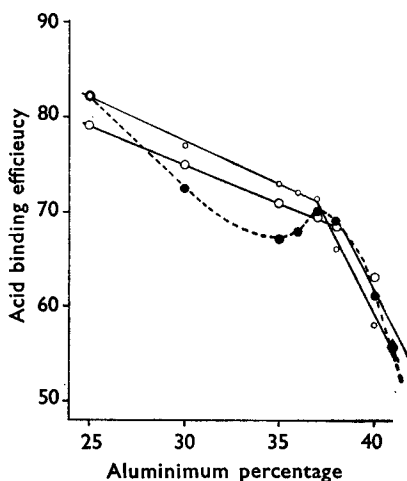


FIG. 2. The variation of acid binding efficiency with aluminium percentage. —○—○— = sucrose modified; —○—○— = glucose modified; --●--●-- = sorbitol modified.

additive is necessary to produce a rise in the neutralising capacity, larger quantities inevitably reduce this because they reduce the aluminium percentage. To eliminate the effect of this reduction in aluminium percentage for purposes of comparison, the "acid binding efficiency" has been calculated. For a compound of aluminium percentage X this can be expressed in the following way.

$$\text{Acid binding efficiency} = \frac{\text{neutralising capacity found}}{\frac{X}{100} \times 1110} \times 100 \text{ per cent}$$

since pure aluminium would have a neutralising capacity of $\frac{3 \times 10,000}{27}$ = 1,110 ml. 0.1N hydrochloric acid per gram. The acid binding efficiency plotted against aluminium percentage gives the curves shown in Fig. 2.

It is clear that the acid binding efficiency increases as the aluminium percentage falls: this happens with increasing amounts of additive. After the maximum neutralising capacity has been reached, the acid binding efficiency falls rapidly. The effect of the additives upon the speed of neutralisation can be seen from Fig. 3, where again decreasing aluminium percentage, i.e., increasing additive, brings about an increase in the speed

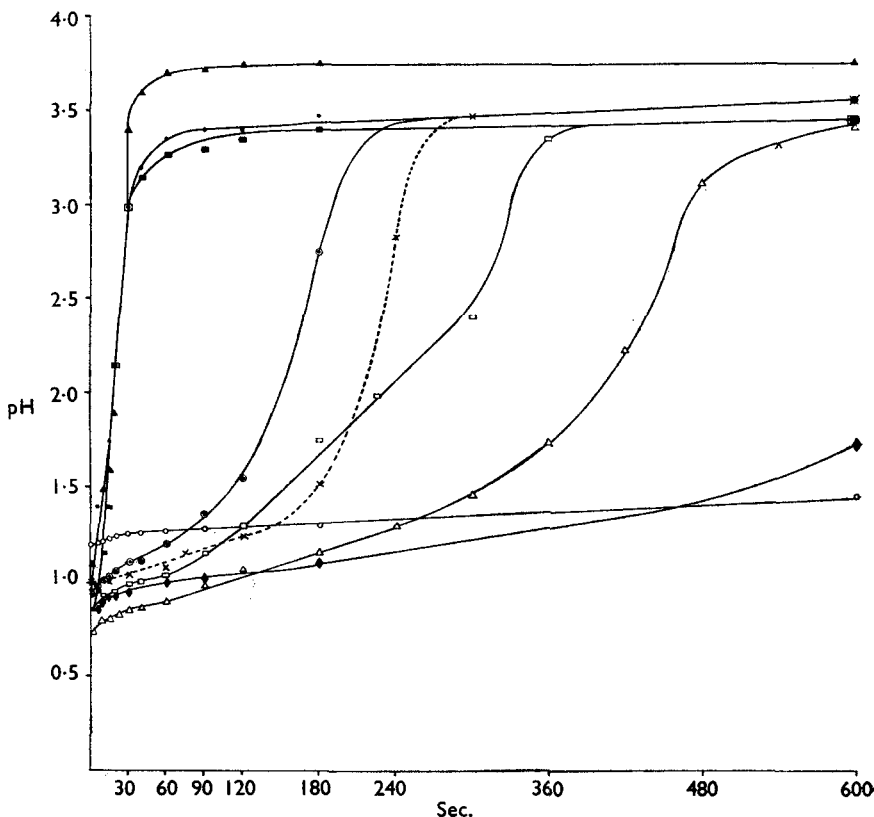


FIG. 3. The speed with which 0.5 g. quantities of the modified aluminium hydroxides react with 50 ml. of 0.1N hydrochloric acid at 37°. Modified $\text{Al}(\text{OH})_3$ with: Sucrose 1/3 M —●—●—; 1/6 M —■—■—; 1/12 M —▲—▲—; 1/24 M —○—○—; 1/48 M —□—□—; 1/96 M —△—△—. No Additive —◆—◆—. $\text{Al}(\text{OH})_3$ ex Xylene —○—○—. Dried Aluminium Hydroxide Gel B.P. - - - X - - - X - - -.

of action. The modified hydroxides are obviously superior to dried aluminium hydroxide gel in this respect; they raise the pH to 3 in 30 sec. as against minutes in the case of the latter. When buffering capacity is plotted against the aluminium percentage the curves shown in Fig. 4 result, and these are similar to those of Fig. 1. On repeated addition of sample to a standard quantity of acid, none of the hydroxides increased the pH of the solution above 4.

To obtain some idea of the behaviour of the modified hydroxides under conditions more closely resembling *in vivo* conditions, some have

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been tested in artificial gastric juice. The results in Fig. 5 show that modified hydroxides are superior to dried aluminium hydroxide gel. They rapidly cause the pH to rise above 3, and maintain the pH in the physiologically desirable range of 3 to 4 for 30 min.

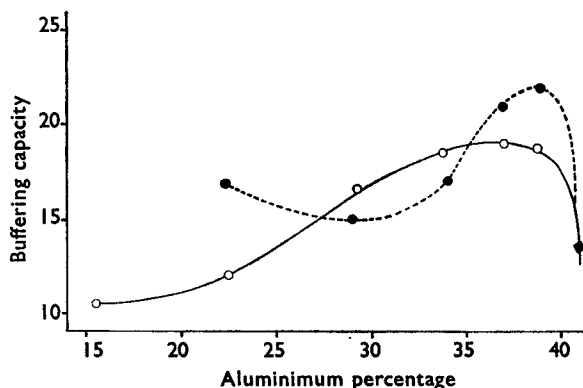


FIG. 4. The relation between buffering capacity and aluminium percentage. —○—○— = sucrose modified; - - ● - - ● - - = sorbitol modified.

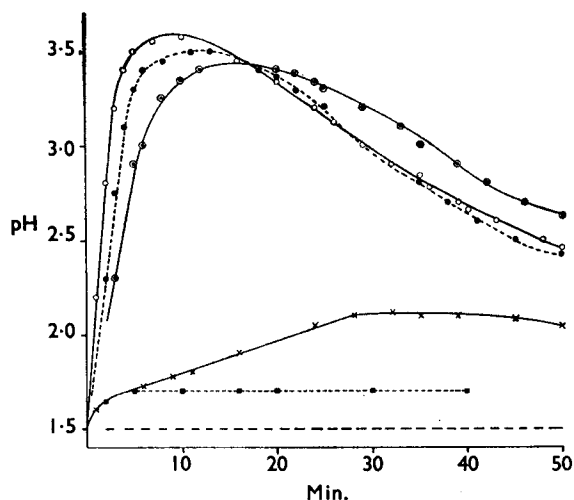
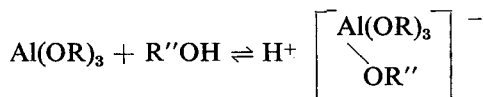


FIG. 5. The behaviour of the modified hydroxides in an artificial gastric medium. —○—○— = sucrose modified; - - ○ - - ○ - - = glucose modified; - - ● - - ● - - = sorbitol modified; - - ■ - - ■ - - = (i) $\text{Al}(\text{OH})_3$ no modifying agent added, and (ii) $\text{Al}(\text{OH})_3$ ex xylene; —X—X— = dried aluminium hydroxide gel B.P.

The modified and unmodified hydroxides are believed to be amorphous, although it is not improbable that some boehmite may occur: this type of structure has been found when samples of amorphous aluminium hydroxide prepared from an aluminium alkoxide are allowed to age in ethanol (Bye and Robinson, 1961) and when aluminium hydroxide is

precipitated from acid solution. Aluminium isopropoxide in isopropanol as used in their preparation, is an acid solution. The alkoxo acid present:



is titratable (Bersin and Meerwein, 1929).

No correlation of the surface area, as determined by the Rigden air permeability method, and the speed of action seems to exist. This method however gives but a relatively crude picture and more refined ideas of surface area are given by the method of low temperature gas adsorption, which may reveal some relation although this method has yet to be applied to our work.

All the products tested were palatable, showing no signs of astringency. Those products deemed suitable as antacids have been granulated and tableted without loss of activity. Samples stored for one year under ordinary atmospheric conditions have shown no loss in the speed of action and neutralising capacity tests.

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The paper was presented by DR. DAVISON. The following points were made in the discussion.

The antacid effect was prolonged by increasing the dosage. The increased effects of the modified hydroxides were thought to be due to increased solubility of the products. A mixture of dried aluminium hydroxide gel, water and carbohydrate did not behave in the same way as the modified products. All the compounds had been tested in the same state of subdivision. Simple static tests can distinguish between products that are unsatisfactory as antacids and products that may be potentially useful, but dynamic tests are needed to simulate more closely gastric conditions. Using low temperature gas adsorption, the surface area of the products has been redetermined, and it was found to be the same for the modified products which reacted rapidly as for the slower-acting aluminium hydroxide from xylene.