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Chemical Reactivity of Aluminium-based Pharmaceutical Compounds used as Phosphate-binders

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Abstract—Several aluminium-containing substances, including antacids used as phosphate-binders in treating renal failure, have been analysed in-vitro under different pH conditions for the release of Al^{3+} ions and for binding of phosphate. Control experiments on different forms of pure aluminium hydroxide validated the methods. At pH 2 it was the most amorphous forms which released Al^{3+} most rapidly. These aluminium ions, available for absorption by the patient, were released from all antacids tested, but no firm phosphate-binding was detected while the pH remained at 2. Phosphate was bound at pH 8, by adsorption onto the surface of aluminium hydroxide. No significant amounts of free Al^{3+} exist in solution at pH 8, since at that pH aluminium hydroxide is precipitated. The most amorphous forms of this solid were the most efficient phosphate-binders. Alumino-silicate salts require prior exposure to acid to produce free Al^{3+} before they can act as phosphate-binders, whereas amorphous aluminium hydroxide acts as an efficient phosphate-binder without prior exposure to acid. Chemical principles are employed to show why aluminium release and phosphate-binding are separate and independent processes. Methods are proposed for maximizing the activity of phosphate- binders in-vivo, while minimising aluminium release.

Patients on maintenance haemodialysis treatment are especially prone to accumulate aluminium. The main sources are the tap-water used to dilute dialysis fluid concentrate, and the administration of aluminium-containing gastric antacids to reduce phosphate absorption from the gut (Alfrey 1986). Now that reverse osmosis is commonly used to remove aluminium from tap water, aluminium accumulation from the continued use of oral antacids has become the major source of aluminium toxicity in dialysed patients (Schneider et al 1986). Although the use of reverse osmosis may permit low dose oral aluminium therapy to continue, it is impossible to be complacent about the continued long-term use of such drugs in the face of accumulating evidence of aluminium absorption from the gut (Fleming et al 1982; Alfrey 1986; Boyce et al 1987). Even if encephalopathy (Alfrey et al 1976) and fracturing osteomalacia (Maloney et al 1982) do not develop, the systemic accumulation of aluminium may have other long-term deleterious effects in the central nervous system (Perl & Brody 1980) and those with impaired renal function and therefore impaired capacity to excrete aluminium are particularly at risk (Recker et al 1977; Santos et al 1986).

The control of diet-derived hyperphosphataemia presents a dilemma, since it requires the oral administration of phosphate-binding drugs. The most effective are aluminium-containing antacids. No potent phosphate-binder which does not contain aluminium has so far been identified. Further, larger doses are employed than in conventional antacid therapy. The relatively long-term consequences and dangers of aluminium absorption must be weighed against the more immediate deleterious results of protracted hyperphosphataemia. It is undetermined to what extent the function of phosphate-binding and aluminium-absorption in the gut are inter-related, if at all. The physicochemical basis for phosphate-binding to aluminium hydroxide is poorly understood.

Several forms of aluminium hydroxide, both reagent grades and pharmaceutical preparations, have been tested in-vitro by chemical methods designed to elucidate the mechanism by which phosphate is bound, and to search for factors which are involved in the absorption by the alimentary tract of ingested aluminium. The experimental methodology takes account of two important aspects of the aqueous chemistry of aluminium. The first of these is the chemical species which predominate at different pH values. These species have been described in a review by Baes & Mesmer (1976). They range from Al^{3+} and $AlOH^{2+}$ through $Al(OH)_3$ and $Al(OH)_4^-$ to $Al_{13}O_4(OH)_{24}^{7+}$. More recently Venturini & Berthon (1987) have studied the stability of those species present in biological fluids under physiological conditions. Al^{3+} ions are strongly hydrolysed in aqueous solution, and which particular species are present at equilibrium is governed principally by the pH. The solid phase $Al(OH)_3$, upon which this study concentrates, is one of these species, and environmental pH will influence its behaviour and physiological effects. The second aspect is the rate of the reaction of aluminium compounds. These rates are a better indicator of their role and effect in-vivo than data based upon equilibrium conditions which will not be attained in the relatively short time the substances are exposed to changing physiological fluids at 37°C, for example as they traverse the gastro-intestinal tract.

A kinetic method has therefore been employed to study the reactivity of various forms of aluminium hydroxide and its precursors. A comparison has been made of their abilities to (i) release Al^{3+} ions, and (ii) bind phosphate ions, under controlled conditions which simulate to some extent the environments which pharmaceutical preparations encounter in the stomach and in the intestine, i.e. at pH of 2 and 8, respectively.

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Materials and Methods

All chemicals were reagent grade, deionized water was used for all solutions and dilutions, and the pharmaceutical preparations were tested in their commercially available forms. The several aluminium compounds were mixed with appropriate reagents in aqueous media of pH 2 or 8, and the reaction mixtures were sampled at various times up to several hours to find the concentrations of aluminium (Al^{3+}) and/or phosphate (PO_4^{3-} or any of its protonated forms). The details are as follows.

(a) For experiments to measure aluminium release at pH 2, reaction commenced when each solid substance (accurately weighed to give approximately 1 mmol L^{-1} of Al) was added to 500 mL of a stirred aqueous solution of 1 mmol L^{-1} NaCl, adjusted to pH 2 with hydrochloric acid, in a thermostat bath ("mixture *A*"). The pH was found to remain constant throughout each experiment (because the OH^- liberated from each substance was considerably less than the H^+ present). At suitable intervals 2 mL samples were withdrawn by pipette and diluted with ice-cold deionized water to "freeze" the reaction. 8-hydroxyquinoline ("oxine") solution was added to the diluted sample to form a coloured complex with the free Al^{3+}. This was extracted into chloroform, and the absorbance at 395 nm was measured.

(b) For experiments to measure phosphate-binding at pH 8, reaction commenced when each solid substance (approximately 0·5 g) was added to 100 mL of a stirred aqueous solution containing 50 mmol L^{-1} KCl and 1 mmol L^{-1} KH_2PO_4, adjusted to pH 8 with potassium hydroxide solution, in a thermostat bath ("mixture *B*"). The pH remained at a value of 8 throughout each experiment. At intervals, 5 mL samples were withdrawn by pipette, centrifuged then filtered through Millipore paper, and 2 mL of the clear solution taken for analysis. The phosphate remaining in solution was converted into reduced molybdophosphoric acid ("molybdenum blue") and the absorbance was measured at 882 nm (BS 2690, 1983).

Pharmaceuticals tested

Manufacturers' specifications (ABPI Data Sheet Compendium, 1986–87):

Alucap (Riker): 475 mg dried $Al(OH)_3$ gel BP per capsule. Aludrox (Wyeth) in tablet form: 282 mg $Al(OH)_3$, $MgCO_3$ co-dried gel, and 85 mg $Mg(OH)_2$ BP per tablet. (Interference from magnesium in the analytical tests on these materials was checked and found to be absent). Antepsin (Ayerst): 1000 mg aluminium sucralfate per tablet. This is a basic aluminium salt of sucrose octasulphate which releases Al^{3+} on hydrolysis. Malinal (Robins) in tablet form: 500 mg almasilate per tablet. This is a complex polymeric aluminosilicate structure related to zeolites, which contains Al^{3+} and Mg^{2+} cations. These cations are released when the aluminosilicate structure is destroyed by acid.

Results

Investigation of release of aluminium

It is known that the reactivity of solid aluminium hydroxide to acid depends markedly upon its crystallinity (Henty & Prescott 1978). The first phase of this work was therefore to measure the rate of release of Al^{3+} from three forms of pure $Al(OH)_3$ with different degrees of crystallinity. These were:

(a) gibbsite, a highly crystalline form of $Al(OH)_3$, prepared by standard methods (Brauer 1963) which allow crystal growth to occur;

(b) amorphous (non-crystalline) $Al(OH)_3$, formed as a sol in aqueous suspension from the hydrolysis of aluminium isopropoxide on contact with water;

(c) partially crystalline amorphous $Al(OH)_3$ gel, obtained by allowing the sol from (b) to form a gel which was dried at 40°C in a rotary evaporator. In this sample some conversion of the amorphous to the crystalline form of the solid had occurred.

Each of these substances was chemically pure $Al(OH)_3$. The amount of Al^{3+} potentially available for release (y mol L^{-1})

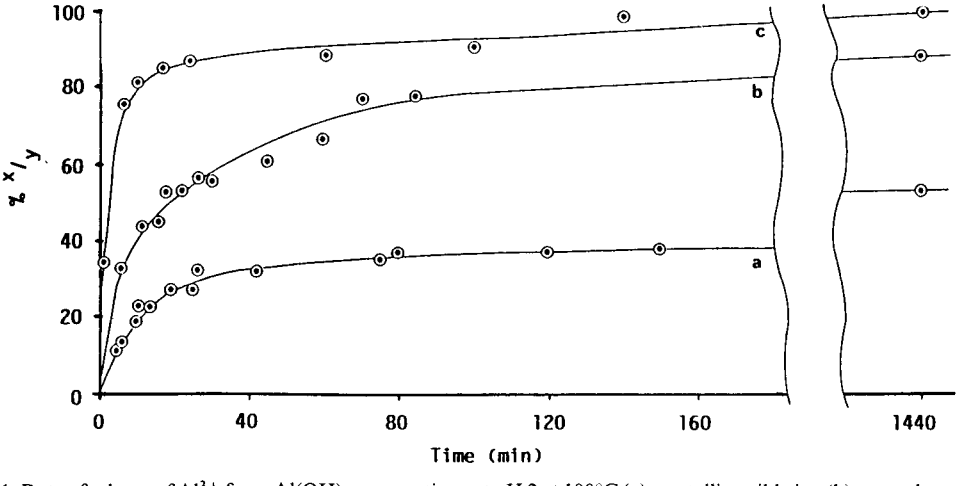

FIG. 1. Rate of release of Al^{3+} from $Al(OH)_3$ preparations at pH 2 at 100°C (a) crystalline gibbsite, (b) amorphous form from aluminium isopropoxide, (c) partially crystalline/amorphous form.

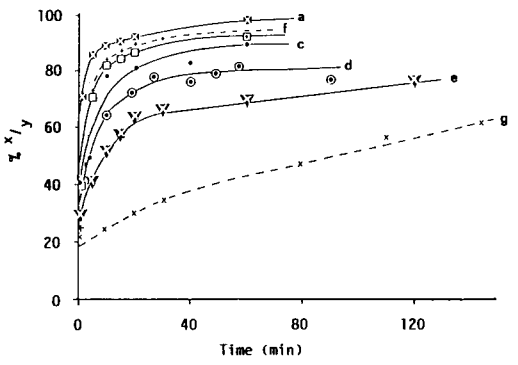

FIG. 2. Rate of release of Al^{3+} from pharmaceuticals at pH 2 at 100°C (a) Malinal, (c) Aludrox, (d) Alucap (aged), (e) Antepsin, and at 37°C (f) Malinal, (g) Alucap (fresh).

was calculated from this chemical formula. Each of them was reacted at pH 2 with mixture *A*, at 100°C to speed up the reaction. The amount of Al^{3+} released at various times was measured (x mol L^{-1}), and the results were expressed as a percentage ratio (x/y).

The rate of release of Al^{3+} from $Al(OH)_3$ is given in Fig. 1 by (i) the slope of the line over the time period 0–20 min, and (ii) the total percentage released after 24 h. Thus the highly crystalline gibbsite is the least reactive, and the amorphous $Al(OH)_3$ freshly precipitated from aluminium isopropoxide is the most reactive. The third preparation, where some crystal growth has occurred during the drying and storage of the amorphous material, shows intermediate reactivity. The more amorphous the solid, the more rapidly is Al^{3+} released by acid.

This "control" experiment established the viability of the analytical technique and gave confidence in applying it to pharmaceutical preparations whose composition was not known with the same degree of precision.

Each of the preparations Alucap, Aludrox, Antepsin and Malinal was reacted as above with mixture *A*, pH 2 at 100°C, and release of Al^{3+} ions was measured. Since no precise chemical formula could be applied to these commercial mixtures, the total Al^{3+} potentially available from each was taken to be the amount actually measured in solution after 24 h reaction at 100°C. The total so measured was used to calculate the ratio x/y.

Fig. 2 gives the results of this analysis, and the following comparisons may be made.

(a) The alumino-silicate Malinal released free Al^{3+} much more rapidly than any of the three $Al(OH)_3$-based preparations in these acid conditions at 100°C.
(b) Of these three preparations, fresh Alucap released free Al^{3+} most rapidly, followed closely by Aludrox. Antepsin was much slower.
(c) A sample of Alucap which had been stored at room temperature for several months released Al^{3+} more slowly than a sample freshly purchased and tested. During the storage period, some crystal growth may occur, reducing the amount of the more reactive, amorphous $Al(OH)_3$ in the capsule.

To simulate physiological conditions more closely, this experiment was repeated on Malinal and fresh Alucap at a temperature of 37°C. Fig. 2 shows the comparison. At the lower temperature Malinal still released Al^{3+} very rapidly, to about 90% of its potential within 20 min. The release from Alucap was much slower at 37°C and reached only about 30% of its potential within 20 min.

Table 1. Percentage of Al^{3+} released from Alucap in the presence of phosphate at pH 2, 100°C.

Phosphate/aluminium ratio	Time (min)							
	1	5	10	15	20	40	60	1440
0:1	40	71	81	84	86		91	100
1:1	37	45	76	81	83	86	89	94
2:1	43	68	82	84	86	87	89	96
3:1	45	66	82	85	87	89	92	96

A modified reaction mixture was used to test for the release of Al^{3+} at the significantly different pH 8. 1·0 g of each of fresh Alucap and Malinal was added to 500 mL of 0·1 mol L^{-1} NaCl adjusted to pH 8 with dilute $NaHCO_3$ solution, at 37°C. Analysis over 24 h showed that less than 1% of the potentially available Al^{3+} was released from each under those conditions, demonstrating their very low solubility in aqueous media at pH 8.

Investigation of phosphate-binding

(a) To test for any interaction between Al^{3+} and phosphate in acidic solution at pH 2, fresh Alucap (0·05 g) was boiled for 1 h with 500 mL of reaction mixture *A* to which 1, 2 and 3 times the molar ratio of phosphate to aluminium had been added. Table 1 shows that the amount of Al^{3+} released and detected in solution is not affected by the presence of phosphate under these conditions. The phosphate concentrations were also measured, and showed no reduction over the period of the experiments. Additionally, 0·05 g samples of Alucap and Malinal were stirred at 37°C for 1 h in mixture *A* with 1 mmol L^{-1} of phosphate. Again no uptake of phosphate was detected. Thus phosphate is not irreversibly bound by Alucap, Malinal, or by the Al^{3+} released from them into aqueous solution, so long as the amounts used are not great enough to raise the pH above 2.
(b) To test for binding of phosphate at pH 8, excess amounts of Alucap (aged and fresh), Malinal, and crystalline and

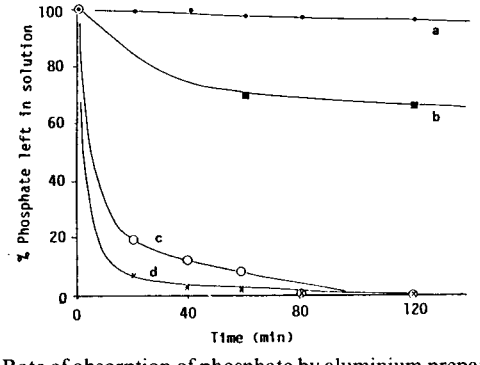

FIG. 3. Rate of absorption of phosphate by aluminium preparations at pH 8 at 37°C (a) gibbsite, (b) Malinal, (c) Alucap, (d) amorphous $Al(OH)_3$ from $Al(OPr)_3$ and $Al(OH)(CH_3CO_2)_2$.

Table 2. Summary of aluminium release and phosphate-binding of two contrasting aluminium-containing antacids.

	Aluminium release			Phosphate-binding		
	pH 2 10 min 100°C	pH 2 10 min 37°C	pH 8 24 h 37°C	pH 2 60 min 100°C	pH2 60 min 37°C	pH 8 60 min 37°C
Antacid						
Alucap—fresh	81%	25%	0%	0%	0%	94%
—aged	64%					91%
Malinal	89%	72%	0%	—	0%	30%

amorphous forms of pure aluminium hydroxide were treated with reaction mixture *B* at 37°C. The phosphate concentration in solution was measured over 3 h. Fig. 3 shows the rate of phosphate uptake from the reaction mixture by each of the substances tested. They may be ranked as follows.

(1) The most efficient phosphate-binder is the amorphous sol of aluminium hydroxide, precipitated instantly when aluminium isopropoxide (or basic aluminium acetate, also tested) comes in contact with an aqueous solution of pH 8. It reduces the phosphate concentration in solution by a factor of 20 in 20 min.
(2) Alucap is very efficient at binding phosphate, reducing its concentration by a factor of 5 within 20 min, and by a factor of 10 in 60 min. There was no significant difference between the aged and fresh samples for phosphate-binding.
(3) Malinal added directly to a solution at pH 8 shows very slow and weak ability to bind phosphate.
(4) Gibbsite, the microcrystalline substance, binds very little phosphate indeed, even in 6 h.

Table 2 summarizes the results obtained with Alucap and Malinal, and emphasises (i) that aluminium ions are not released at pH 8, and (ii) that phosphate is not permanently or strongly bound at pH 2. Although showing least phosphate-binding in-vitro at pH 8, Malinal is capable of most phosphate-binding in-vivo, since free Al^{3+} ions released by acid in the stomach will reprecipitate as amorphous aluminium hydroxide at pH 8 on reaching the intestine.

Discussion

From the results described, it is suggested that the mechanism for binding phosphate by aluminium compounds is not a chemical one involving, for example, coprecipitation or other coagulation of free Al^{3+} ions with phosphate ions directly in the solution phase. It is proposed instead that the mechanism involves a process of adsorption of phosphate on to the surface of solid aluminium hydroxide at pH 6–8. This adsorption will occur most readily when the specific surface area of the solid is as large as possible, as is the case when a sol is freshly precipitated. So the amorphous sol was found to be the most efficient phosphate-binder. By contrast, gibbsite, the crystalline form of the solid has a small specific surface area, and was a very inefficient phosphate-binder. Adsorption is probably due to the strongly basic surface OH groups of the aluminium hydroxide attracting protons from solution, creating positively charged sites. To these, the negative ions HPO_4^{2-} and $H_2PO_4^-$ will be attracted and bound firmly, especially HPO_4^{2-}, the ion which predominates at pH 8 (Mikami et al 1983). A further ligand exchange process on the surface may then lead to chemical bonding of the phosphate to the aluminium ion via its oxygen atoms, resulting in the replacement of water ligands by phosphate.

This adsorption mechanism is described in the work of Kwong & Huang (1978, 1979) on anion adsorption by hydrolysed aluminium salts. Their studies showed phosphate adsorption phenomena similar to ours, over a pH range of 4 to 8. Measurements of the surface area of the freshly precipitated hydroxide correlated with phosphate-binding capacity under different conditions, and pointed to this mechanism of adsorption. Their work attracted the interest of water engineers because alum is widely used in water purification.

A recent study by Balasa et al (1987) compared the phosphate-binding capacities of several liquid and solid aluminium hydroxide gel antacids at different pH. Significant "interbrand" differences were observed and it was shown that pH affected phosphate uptake. However, at variance with our observations is their statement that phosphate-binding was most efficient for most gels at pH 2. Scrutiny of their conditions reveals that the relative amounts of hydroxide to acid present, especially at pH 2 and 3, would not allow these pH values to remain constant throughout their experiments, but pH would rise to near neutral values when the alkali reacted with the acid. Thus the most efficient binding of phosphate was not occurring at pH 2 or 3, but was probably occurring on the surface of aluminium hydroxide being freshly precipitated as the pH increased. Our results demonstrate that these are the optimum conditions for binding of phosphate, and that this binding occurs at pH near neutral.

Larson et al (1986) also conducted a study which resembles ours in some respects. Phosphate-binding was measured for five different proprietary aluminium hydroxide gels, and for gibbsite and boehmite, after 3 h at pH 7·5 preceded by 15 min at pH 3. The reactivity of the substances to acid itself at pH 2 and 3 (i.e. the "antacid" reaction) was also measured, and the release of free Al^{3+} ions was inferred from this measurement. Different reactivities were explained on the basis of different surface areas of the substances. There was a correlation between measurements of surface area and phosphate-binding for gibbsite and boehmite, and they deduced an adsorption mechanism. In explaining phosphate-binding by antacids which had previously dissociated in acid conditions, they believed that in addition to phosphate adsorption on to the surface of aluminium hydroxide, aluminium ions and phosphate ions reacted together at acid pH to form an insoluble aluminium phosphate. Our results gave no evidence of this precipitation, but in their work the large excess of aluminium hydroxide used would alter the situation. Some neutralization of the acid would occur, and the undissolved aluminium hydroxide would provide surface upon which phosphate could be adsorbed and precipitated.

This work has led us to propose the following model describing the events taking place when aluminium hydroxide is ingested for the purpose of phosphate-binding in-vivo. In the ordinary acidic conditions of the stomach, reaction occurs to release a certain amount of free Al^{3+} ions. Some of this Al^{3+} may be absorbed here, but most of it will pass through the gut, where the lumen pH increases rapidly

to about 6 and remains between 6 and 8·5 in the distal intestines. In this pH range, Al^{3+} is freshly reprecipitated as colloidal, amorphous aluminium hydroxide. Phosphate is now rapidly absorbed onto the large surface area of this amorphous solid. The aluminium hydroxide, with phosphate absorbed, will pass unchanged through the intestine, because the pH distally would not decompose it, and eventually it will be excreted in the faeces. On the basis of this model, a good phosphate-binder will absorb phosphate near the beginning of the intestinal tract before much phosphate becomes absorbed into the body through the jejunum. In a slightly modified model, any acid phosphate-aluminium complexes formed at low pH (Akitt et al 1971) would also precipitate out when the pH rises to around neutral values.

The effectiveness of aluminium-based antacids which have been used for the binding of intestinal phosphate in chronic renal failure may now be compared. The main factor affecting potency is the availability of amorphous aluminium hydroxide at the beginning of the small intestine. This amorphous solid is in its most active form when freshly precipitated from the free Al^{3+} produced from the dissolution of such antacids in the stomach. On this basis, therefore, the substances which release free Al^{3+} most rapidly at pH 2 and 37°C would generate the largest amounts of the most effective phosphate-binder at pH 8. From Fig. 2 it is evident that Malinal, releasing almost all its Al^{3+} within 20 min, is the most effective if this model involving prior release of Al^{3+} is correct. If, however, Malinal were to pass unchanged into the small intestine at pH 8, Fig. 3 shows that it would not be an effective phosphate-binder. It therefore owes its effectiveness to the prior release of Al^{3+} in the stomach.

For Alucap (and probably for other similar pharmaceutical preparations of aluminium hydroxide) Fig. 2 shows that at pH 2 and 37°C about 70% of it did not dissolve within 20 min. Passing from the stomach into the gut therefore, this undissolved Alucap would be available for phosphate-binding, along with the smaller amount of aluminium hydroxide freshly reprecipitated from the Al^{3+} out of the Alucap which did dissolve in the stomach. Now reference to Fig. 3 shows that Alucap itself, with no pretreatment, binds phosphate from solution at pH 8 almost as efficiently as the aluminium hydroxide precipitated in-situ. This implies that most phosphate would be taken up by the larger amount of undissolved but very active Alucap, because the binding itself does not depend on prior solution and reprecipitation. Consequently the overall in-vivo phosphate-binding capacity of Alucap is probably similar to that of Malinal, although there is a large difference in the amounts of free Al^{3+} released from each at low pH and 37°C. Malinal will not function as a phosphate-binder without prior exposure to acid, whereas this is not necessary with Alucap.

The other major factor to consider in this assessment is the toxicity of aluminium itself. It is well recognized that the gastrointestinal tract represents a formidable barrier to aluminium absorption (Kaehny et al 1977). Many workers believe that the major route for the absorption of aluminium is through the stomach and adjacent duodenum at low pH (Ihle & Becker 1985; Alfrey 1986). This is in accord with speciation studies which show that aluminium in solution is predominantly in monomeric form at low pH (Baes & Mesmer 1976). Such monomeric Al^{3+} would be more bioavailable than polymeric or solid forms which exist at higher pH, so that transport through membranes and interaction with proteins, perhaps via citrate and other complexes (Martin 1986), occurs more readily at low pH. Since Alucap releases much less monomeric Al^{3+} at low pH than does Malinal, absorption of aluminium from Alucap would be correspondingly less, making it a much less toxic drug which still shows a very high phosphate-binding capacity. For Malinal, free aluminium ion release must precede phosphate-binding. For Alucap and related antacids, phosphate-binding does not depend on prior release of Al^{3+}, although it may be enhanced by it.

A final point worth noting is that the amorphous form of aluminium hydroxide is less stable than its crystalline form, of which gibbsite is the ultimate example. So during storage of the amorphous material over a period of months, some crystal growth will occur unless efficient inhibitors of crystal growth are present. Such crystallinity would cause a reduction in the reactivity of the material. One of the tests on Alucap at pH 2 and 100°C demonstrated this point: less Al^{3+} was released by acid from the aged samples. However, tests on Alucap at pH 8 and 37°C showed no significant difference in phosphate-binding between fresh and aged samples. At this lower temperature, and where there was an excess of the aluminium hydroxide, any difference in crystallinity is not great enough to affect the rate of uptake of phosphate.

In summary, from the viewpoint of phosphate-binding, the pharmaceutical desideratum would be to deliver aluminium hydroxide in its most amorphous form into the proximal small intestine, while avoiding exposure to low gastric pH in order to minimize aluminium release.

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