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The determination of aluminium in antacid formulations by Gran's Plot titration with sodium fluoride

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The aluminium content of a number of proprietary antacid formulations has been determined by titration with sodium fluoride, using the fluoride activity electrode as an end-point detector. Results compared favourably with the official method. The fluoride titration, however, involved less sample manipulation and was more rapid to carry out. End-point detection was made easier by treating titration data by the Gran's Plot method.

The British Pharmacopoeia (1973) assay for aluminium hydroxide Gel B.P. determines Al^{3+} by a complexometric titration. In this procedure, which is relatively time-consuming and involves a number of manipulations, the sample is first digested in dilute mineral acid and then heated for thirty minutes with excess sodium edetate to ensure complete formation of the aluminium edetate complex. The excess edetate is then determined by titration with lead nitrate. Potentiometric titration methods for the determination of aluminium have been described by Chirkov (1948), using fluoride as titrant and aluminium and platinum electrodes, and by Jaselskis & Bandemer (1969), using a fluoride activity electrode as an end-point detector. Gran's Plot (Gran 1952) titration of aluminium with sodium fluoride (Orion Research 1971) enables the titration end-point to be more conveniently detected with the fluoride activity electrode and is readily applicable to the determination of aluminium in both solid and liquid antacid formulations.

MATERIALS AND METHODS

Apparatus

An Orion 701 digital pH/mV meter was used in conjunction with an Orion double liquid junction Ag/AgCl reference electrode and a fluoride activity electrode (Activion Glass Ltd). Results were graphed on Orion 10% volume-corrected Gran's Plot paper.

Reagents and solutions

Aluminium chloride hexahydrate (Koch-Light Ltd) was used to prepare a 10^{-3} M Al^{3+} solution standardized by titrating the chloride. The titrant was 0·05 M sodium fluoride (Analar). The ionic strength/pH adjusting solution (ISA) was 2 M acetate buffer, containing sodium acetate (82 g) and glacial acetic acid (57 ml) in 1 litre, both reagents being Analar grade.

Gran's plot

The fluoride activity electrode exhibits a Nernstian, or near Nernstian, response to changes in fluoride ion concentration at constant ionic strength. Thus,

$$\text{Electrode Potential (E)} \propto \log [F^-]$$

and

$$\text{Antilog E} \propto [F^-]$$

On semi-antilog paper a plot of E versus $[F^-]$ will result in a straight line. However, during the course of the titration, addition of fluoride titrant changes the volume of the solution, thus affecting the fluoride concentration sensed by the electrode. Skewing the horizontal axis of semi-antilog paper upwards by 10% corrects for a volume change of up to 10% and allows linear titration plots of E vs titre to be made (Fig. 1). A significant feature of the Gran's plot titration is that electrode potentials corresponding to addition of fluoride aliquots past the end-point are graphed, and the resulting straight line extrapolated back to the horizontal axis to give the end-point titre.

Analysis

Antacid suspensions were diluted volumetrically 1 in 1000 with distilled water to give an aluminium concentration in the region of 10^{-3} M. An automatic micropipette (50 μl) with non-wettable plastic tip was used to ensure complete transfer of the sample. For solid formulations, a weight of powder equivalent to one tablet was diluted with distilled water to again give an aluminium concentration of about 10^{-3} M. Before the analysis of samples, a blank and a standard solution were titrated with fluoride.

(i) *Blank titration.* ISA (1 ml) was added to distilled

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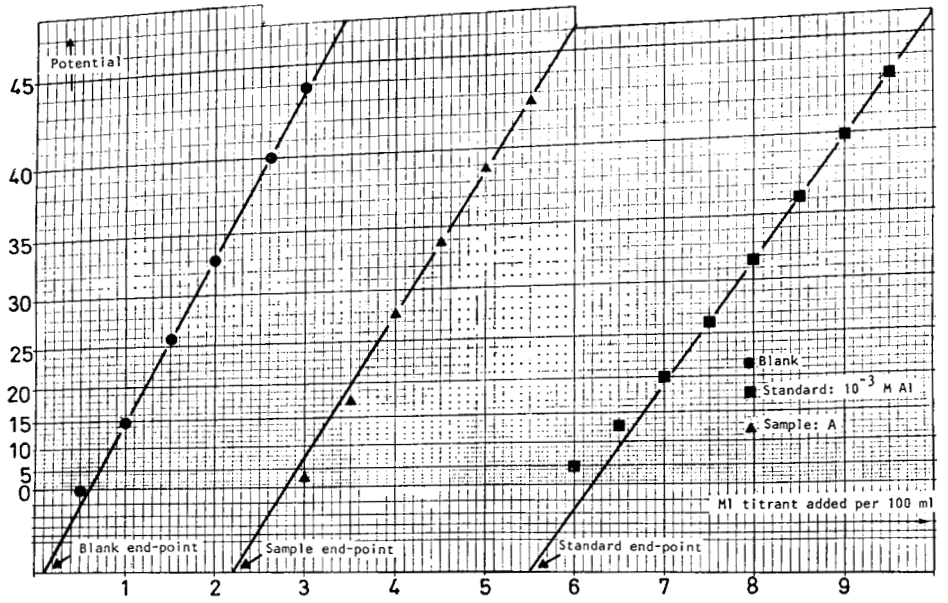

FIG. 1. Data from titration of aluminium with sodium fluoride plotted on 10% volume-corrected Gran's plot paper. ●, blank; ■, standard 10^{-3} M aluminium; ▲, sample A. Ordinate: potential. Abscissa: titrant added (ml/100 ml).

water (100 ml) and fluoride titrant (0·5 ml) added to the stirred solution. The meter was set to read zero with the fluoride/reference electrode couple, and further 0·5 ml fluoride aliquots added. The electrode potential was plotted against titre on 10% volume—corrected Gran's plot paper scaled so that the 5 ml reading fell near the top of the anti-log axis. The resulting straight line was extrapolated back to the horizontal axis to give the blank end-point.

(ii) *Standard titration.* ISA (1 ml) was added to 10^{-3} M Al^{3+} standard solution (100 ml) and titrated with fluoride as before. When the potential displayed by the meter became negative, fluoride was in excess. The potential corresponding to each 0·5 ml aliquot of titrant added past this point was recorded and results plotted as before. Extrapolation of the resulting straight line to the horizontal axis gave the standard end-point.

(iii) *Sample titration.* ISA (1 ml) was added to the appropriately diluted sample (100 ml) and the solution titrated with fluoride. When fluoride titrant was in excess, the potential became negative and meter readings stabilized rapidly. Results were treated as for the standard titration, extrapolation back to the horizontal axis giving the sample end-point.

Calculation

The molarity of aluminium in the sample solution was found from equation 1, and hence the concentration of aluminium in the original sample could be calculated.

$$\text{Eqn 1} \quad \frac{\text{sample concn}}{\text{standard concn}} = \frac{\text{unknown intercept—blank intercept}}{\text{standard intercept—blank intercept}}$$

RESULTS AND DISCUSSION

Aluminium hydroxide Gel B.P. contains between 3·5 and 4·4% w/w Al_2O_3, equivalent to 95·8 mg to 120·5 mg Al^{3+} per 5 ml. Six replicate analyses on a sample were carried out by the fluoride titration and official methods. Results from both methods were found to be comparable, the official method giving a mean aluminium concentration of 117·9 mg per 5 ml and the fluoride titration method a mean of 116·4 mg per 5 ml. The standard deviation for the fluoride method was 0·75 and the standard error of the mean 0·34, indicating a satisfactory level of precision.

The accuracy and precision of the fluoride titration method having been established, the aluminium contents of proprietary antacid preparations, the formulae of which are given in Table 1, were determined. Preparations A and B were liquids, whereas C and D

were tablet formulations. In all cases results were comparable to the official method (Table 2). Magnesium hydroxide present in the various formulations did not interfere with the assay.

The major advantages of the fluoride titration method are that it is quick and easy to perform. If a number of different samples are to be analysed it is unnecessary to perform a blank and standard titration in every case. Once the meter has been calibrated, one blank and one standard are sufficient for all subsequent determinations. Thus, effectively, each sample is analysed by one titration. Sample manipulation is reduced to a simple dilution in order to give an aluminium concentration compatible with the range of the fluoride electrode. An aluminium concentration of about 10^{-3} M proved generally suitable. Typical analysis times were in the region of 8 min per sample. A further simplification is the omission of the initial acid-digestion step used in the official method.

Table 1. Formulae of the various preparations analysed.

	A*	B*	C†	D†
Dimethicone	20	125	250	20
Magnesium hydroxide	200	100	—	200
Aluminium hydroxide gel B.P.	—	4·75 §	—	—
Dried aluminium hydroxide gel B.P.	200	—	500	200

* mg per 5 ml. † mg per tablet. § ml per 5 ml.

Table 2. Comparison of the fluoride titration and official methods for the determination of aluminium in various antacid preparations.

	Fluoride titration	B.P. method
A*	51·3	50·8
B*	109·6	110·8
C†	132·4	133·7
D†	52·9	52·4

Aluminium concentration: * mg Al^{3+} per 5 ml
† mg Al^{3+} per tablet

The reaction between fluoride and aluminium is ionic, and has been studied by Srinivasan & Rechnitz (1968), and by Jaselskis & Bandemer (1969) who found that the reaction was complex and that the stoichiometry varied with pH and aluminium concentration. At pH 3·8 the stoichiometry was about 2·15 to 1 fluoride to aluminium. In the present investigation the stoichiometry at pH 4·6 was 2·7 to 1, in agreement with that found under similar conditions by a previous study (Orion Research 1971).

Aluminium in antacid formulations is present in non-ionic form, as hydrated aluminium oxide. The sample solution, though, may be regarded as a saturated solution of Al^{3+}, the concentration of which in solution is consequently very small. Each addition of fluoride titrant, before the end-point, causes a large and rapid negative shift in potential due to excess F^- in solution. The potential then shifts back towards the positive direction as fluoride in solution is used up by reaction with Al^{3+}, thus allowing further aluminium to go into solution. This process continues until the end-point, when all the aluminium is used up and fluoride is in excess. As the fluoride concentration of the solution rises, steady meter readings are obtained and these data are used in the Gran's plot. Bad data points, which generally occur just past the end-point when the fluoride concentration is low and the electrode is operating near its sensitivity limit, are easily seen and discarded.

The titration of aluminium with sodium fluoride offers a convenient method for the determination of aluminium in antacid formulations. End-point detection with the fluoride activity electrode is simplified by use of the Gran's plot method.

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