THE SEPARATION AND VOLUMETRIC DETERMINATIONS OF ALUMINIUM, BISMUTH, CALCIUM AND MAGNESIUM, IN PHARMACEUTICAL PREPARATIONS

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During recent years the number of pharmaceutical preparations containing aluminium, bismuth, calcium and magnesium in various combinations has increased considerably, and thus the problem of the rapid determination of these elements in the presence of one another has become correspondingly important. The wealth of literature describing the determination of individual metal ions with ethylenediaminetetra-acetic acid naturally led to a consideration of this reagent.

As ethylenediaminetetra-acetic acid (EDTA) is capable of chelating with a large number of metal ions care must be taken that the conditions under which it is used are so chosen that the interference with the determination of one ion by others present is a minimum. The published data on stability constants of the various metal complexes may assist in devising methods for selective determinations, but the constants will almost certainly have been determined in an arbitrarily arranged set of conditions, and they may be considerably modified in practice. There are three main lines of approach to the problem, namely (i) control of *p*H, (ii) use of specific indicators and (iii) use of masking agents; that is, reagents which will, under given conditions, react with certain metal ions to form complexes more stable than those formed with EDTA under the same conditions, thus leaving other ions free to be titrated. Much work remains to be done especially in the search for specific indicators, but considerable advances have been made, particularly as a result of the systematic studies of Přibil and others.

These considerations have now been applied to the analysis of pharmaceutical preparations containing aluminium, bismuth, calcium and magnesium. The determinations of calcium and magnesium in the absence of other metals are already well known and require only passing comment. It was necessary, however, to examine the various methods which have been suggested for the determination of aluminium and of bismuth to select those most suitable for inclusion. Certain difficulties, not mentioned in the literature, were encountered, necessitating a more detailed study of the conditions of reaction. These two metals are therefore dealt with individually before the problem of separation is discussed.

Aluminium

Most methods which have been suggested for the volumetric determination of aluminium with EDTA depend upon the addition of a known excess of the reagent to a solution of the metal followed by titration of the excess with a standard solution of some other metal for which a

reliable indicator is available; ferric chloride[1,2], thorium nitrate[3,4], and zinc chloride[5] have all been used for this purpose. More recently a method of direct titration using hæmatoxylin as indicator has been suggested by Taylor[6].

For routine application to the present work it seemed that the thorium nitrate method showed the greatest promise, because it could also be used to determine aluminium and bismuth together, and because thorium nitrate solution is stable and reliable for use as a standard. It was therefore decided to examine ter Haar and Bazen's[4] procedure in detail, despite the fact that they reported the reaction between aluminium and EDTA to be nonstoichiometric and to yield results which were consistently low to the order of about 1 per cent.

Experimental

A number of standard solutions of aluminium prepared from different grades of the metal were analysed by the slightly modified ter Haar and Bazen's procedure described below and by the gravimetric oxine method[7] (Table I). The effects of varying the excess of complexing agent added (Table II), the time for which the reaction was allowed to proceed (Table III) and the temperature of the reaction were also examined. In addition, two of the solutions were used to examine the direct titration method proposed by Taylor[6].

TABLE I

APPLICATION OF THE METHOD OF TER HAAR AND BAZEN TO STANDARD ALUMINIUM SOLUTIONS

	Theoretical Al content (g. per litre)	Al found		Per cent. recovered by EDTA method
		By EDTA*	By oxine	
Solution 1 (prepared from 99·99 per cent. Al)	1·666	1·665		99·9
Solution 2 (prepared from 99·99 per cent. Al)	1·636	1·638	1·652 1·640	100·1
Solution 3 (prepared from 99·8 per cent. Al)	1·623	1·623	1·626 1·641	100·0
Solution 4 (prepared from 99·5 per cent. Al)	1·781	1·776†	1·785 1·791	99·7

* The results obtained using EDTA are based on the mean values obtained from four titrations on each solution. In no case did a burette reading in any of the groups differ by more than 0·05 ml. from the mean value.

† Corrected for the presence of 0·25 per cent. of Fe.

*Method of ter Haar and Bazen**

To a quantity of solution containing from 15 to 20 mg. of aluminium add 25 ml. of 0·1N EDTA and 80 ml. of water; neutralise to congo red paper by the dropwise addition of solution of sodium hydroxide and add 5 ml. of 2M monochloroacetic acid, 10 ml. of 1M sodium acetate and 1·5 ml. of alizarin S indicator. Titrate with 0·1N thorium nitrate to the

* The reagents used in the above and all subsequent determinations described are classified as an Appendix.

TABLE II

EFFECT OF VARYING THE EXCESS OF EDTA ADDED IN THE METHOD OF TER HAAR AND BAZEN

0·1N EDTA added (ml.)	Amount theoretically required (ml.)	Amount used (ml.)	Per cent. deviation
50	6·74	6·70	−0·6
40	13·48	13·44	−0·3
35	13·48	13·46	−0·2
25	13·48	13·44	−0·3
25	6·74	6·76	+0·3
25	12·92	12·92	0
20	12·92	12·88	−0·3
15	12·92	12·70	−1·7
15	13·48	13·22	−1·9

bluish-red end-point; each ml. of 0·1N EDTA is equivalent to 0·001349 g. of Al.

In order to examine the effect of temperature on the reaction, solutions were boiled and maintained as near the boiling point as possible during titration. They gave almost identical results with those quoted in Table I.

TABLE III

THE EFFECT OF TIME OF REACTION BETWEEN AL AND EDTA

Time*	Per cent. deviation of the result from the theoretical value	
	Using a twofold excess of EDTA	Using only a slight excess of EDTA
30 seconds	−3·9	−9·1
1 minute	−0·6	−2·2
4 minutes	+0·3	−1·5
15 minutes	−0·1	−0·7
30 minutes	+0·1	+0·2

* The time recorded here is from the end of the addition of EDTA to the commencement of the titration. In practice this time would be somewhat more than a minute; the above figures were obtained by having all solutions measured for addition before commencement of the reaction and by knowing in advance the exact amount of sodium hydroxide required for neutralisation.

The effect of certain ions likely to be present in pharmaceutical preparations when determining aluminium was examined experimentally. Under suitable conditions bismuth reacts quantitatively and reference is made to this in a later section; calcium and magnesium do not interfere; sulphates cause interference with the end-point when present in large excess; phosphates, which may be present in certain tablets, cause precipitation of thorium and must therefore be removed; the effect of silicate in solution has not yet been examined, although it has been removed by the classical gravimetric procedure before determination of the metal ions. Common excipients such as lactose, sucrose, starch, tragacanth and acacia are without effect on the determination, but it was found to be easier to remove insoluble matter by filtration or by ignition before proceeding to the titration.

Direct Titration Method of Taylor

A number of determinations by the method of Taylor[6] were made on two of the aluminium solutions prepared during the examination of the thorium nitrate method. This direct titration procedure is carried out by adding the almost neutral aluminium solution, the strength of which is to be

determined, from a burette to standard EDTA containing hæmatoxylin indicator until a permanent pinkish-purple colour is obtained. The titration liquid is then buffered to *p*H 6·0, boiled and titrated with the aluminium solution to the return of the pinkish-purple end-point, the temperature being maintained above 70° C. It was found that a sharper and more satisfactory end-point could be obtained by titration with the aluminium solution to within 0·5 ml. of the equivalence point before addition of the buffer solutions and boiling. This demands an approximate knowledge of the titre to be expected, obtained by a preliminary titration carried out as described by Taylor. The series of results listed in Table IV were obtained in this manner.

TABLE IV

APPLICATION OF THE METHOD OF TAYLOR TO STANDARD ALUMINIUM SOLUTIONS

	Theory	Content of aluminium (g./l.)	
		Found	Per cent. deviation
Solution 1	1·666	1·658	−0·5
		1·673	+0·4
		1·662	−0·2
		1·676	+0·6
		1·653	−0·8
Solution 2	1·636	1·632	−0·2
		1·623	−0·8
		1·628	−0·5
		1·633	−0·2

DISCUSSION

The results listed in Table I show that, under the conditions proposed, theoretical amounts of aluminium have been found. This observation is at variance with that of ter Haar and Bazen who reported results which were consistently low to the order of about 1 per cent. It has been demonstrated that low results may be obtained if an insufficient excess of complexing agent is added, or if the time of reaction is insufficient, and, following from this, the smaller the excess of EDTA added the longer the time required for the reaction to proceed to completion. These results show that the reaction between aluminium and EDTA is a relatively slow one, and explain one of the principal difficulties which has been encountered in devising a suitable direct titration. If a twofold excess of EDTA is added to the aluminium solution the reaction may be assumed to be complete well within the time required to neutralise and add the buffer solutions and indicator.

The direct titration using hæmatoxylin as indicator yields results which may vary within about 1 per cent. of the theoretical figure, but there is no indication that they are consistently low. For routine purposes the method suffers from the disadvantages that the sample solution must be placed in the burette, that the titration must be carried out in hot solution and that so unsatisfactory a material as hæmatoxylin must be used as indicator. In one respect the use of hæmatoxylin as indicator is of value in that the formation of the aluminium-hæmatoxylin lake at the end-point confers a degree of specificity. A reasonable balance between accuracy, convenience and specificity must be maintained, however, and it is therefore considered that the thorium nitrate method should be applied in general routine practice, whilst the direct titration procedure is of value in the

occasional instances when a pharmaceutical preparation of aluminium also contains sulphate or phosphate.

Bismuth

Methods which have been suggested for the titration of bismuth with EDTA include amperometric titration[8], back-titration with standard magnesium solution at *p*H 10[9], direct titration using the thiourea complex as indicator[10,11], back-titration with thorium nitrate at *p*H 3·5[12], direct titration using potassium iodide as indicator[13] and direct titration using catechol violet as indicator[14]. Since a high degree of accuracy was claimed for the majority of these methods it was decided to concentrate on those which are more likely to be specific. Pre-eminent in this category is the method using catechol violet, an acid-base indicator[15] which is yellow in acid, and deep blue in moderately alkaline media, forming a deep blue complex with bismuth at *p*H 1 to 2; few other metals chelate with EDTA at this degree of acidity and the method is therefore considerably selective; the colour change is specific for bismuth at this *p*H. The procedure described by Grönkvist[10] was also selected for examination since the formation of the yellow-coloured bismuth-thiourea complex also serves to confirm the presence of bismuth; this method suffers from the disadvantage that, since the titration is carried out at *p*H 2·5 to 4·0, other metals may also chelate with the titrant. More recently Fritz[11] has suggested modifications to the method which render it more selective. Some determinations were also made by the back-titration method using thorium nitrate as described for aluminium.

Experimental

A standard solution of pure bismuth metal (99·995 per cent.) in nitric acid was prepared for an initial comparison of the methods. The thiourea procedures of Grönkvist and of Fritz were applied exactly as stated by the authors. Considerable modifications were necessary, however, to the outline procedure suggested by Malát, Suk and Ryba[14] using catechol violet before a satisfactory titration, free from precipitation of bismuth and fading of the indicator, yielding a sharp end-point, could be obtained. Attention was drawn by these authors to the instability of catechol violet in strongly alkaline solutions, but no mention was made of its instability in strongly acid media or its destruction by strong oxidising agents; these features, taken in conjunction with the facts that the end-point is much sharper in relatively dilute solutions, but that precipitation of bismuth is likely to take place in all but quite acid solutions, has made it necessary to adopt the following procedure:—

Dilute a suitable aliquot of the solution in nitric acid, containing about 120 mg. of bismuth, to 50 ml. with water ensuring that only sufficient acid is present to prevent precipitation of the metal. Add 2 drops of catechol violet indicator and, if the solution is violet in colour, add dilute solution of ammonia drop by drop until the characteristic deep blue colour is obtained. Titrate with 0·1N EDTA until the solution turns violet-red, dilute with 200 ml. of water, adding a further 6 to 8 drops of the indicator

solution (the solution reverts to its original blue colour on dilution) and continue the titration. The colour of the solution changes through violet, red and orange, followed by a sharp change to bright yellow at the end-point; each ml. of 0·1N EDTA is equivalent to 0·01045 g. of Bi.

By adopting this procedure the necessary dilution required for a sharp end-point may be made without danger of precipitating the bismuth, since the majority of this is complexed by the time the additional water is added.

Table V records the results obtained by these various methods on a standard bismuth solution.

TABLE V

THE DETERMINATION OF A STANDARD BISMUTH SOLUTION BY VARIOUS METHODS

	Content of Bi (mg. per 10 ml.)
Theoretical figure	124·6
By precipitation as phosphate[16]	124·9
By Catechol Violet method	124·0
By method of ter Haar and Bazen	124·0
By method of Grönkvist	124·3
By method of Fritz	124·0

The determination with catechol violet suffers from the disadvantage that even small quantities of strongly oxidising agents seriously impair the end-point; chlorides, for example, must be absent from the nitric acid solutions, organic materials giving rise to oxides of nitrogen when dissolved in nitric acid are deleterious and so is the presence of hydrogen peroxide. In general, however, solutions may be prepared from most pharmaceutical preparations so that these interfering substances can be avoided. The method of Fritz gives a good end-point, although not so sharp as that with catechol violet, but the precise *p*H adjustment necessary makes this determination a somewhat lengthy one compared with the catechol violet method. Grönkvist's procedure suffers from a number of disadvantages:

(i) Since it is carried out at *p*H 2·5 to 4·0 it is subject to interference from a number of other metal ions.

(ii) The end-point is by no means as definite as in the other methods described.

(iii) Precipitation of phthalic acid has been encountered during titration on a number of occasions and this may make the end-point more difficult to detect.

DISCUSSION

These considerations point to a clear choice of the catechol violet method for the majority of pharmaceutical materials. Only in those instances where an oxidising mixture cannot be avoided is it suggested that the thiourea method be employed; as will be seen from the applications in a later section this has not been necessary in any of the work carried out.

THE DETERMINATION OF ALUMINIUM, BISMUTH, CALCIUM AND MAGNESIUM IN THE PRESENCE OF EACH OTHER

The methods which have been employed in this scheme of separation are based upon the above procedures and upon joint determinations, that is, determination of two metals together, and masking techniques. For

example, bismuth and aluminium may be determined together by the thorium nitrate method, bismuth and magnesium or bismuth and calcium, by a modification of the usual solochrome black titration in alkaline solution. If both calcium and magnesium are present as well as bismuth, the bismuth may be removed rapidly by precipitation as oxychloride. Several attempts were made to mask bismuth so that magnesium and calcium might be obtained without having to carry out a separation, but these have so far been unsuccessful. Very recently, however, Přibil and Roubal have described the use of 2:3-dimercaptopropanol for this purpose[17] and the possibility of applying this method to the present scheme is now under consideration.

Aluminium in the presence of magnesium or of calcium is more easily masked since, under suitable conditions, it is effectively complexed with triethanolamine[18,19]. One or two cautionary notes must be added concerning the methods, however, and these are mentioned below with the recommended procedures. Detailed methods for the various separations and joint titrations are described, together with results of some of the experimental work. The method given for the removal of bismuth is considered to be an improvement on that described in the British Pharmaceutical Codex for Compound Lozenges of Bismuth, since traces of bismuth may remain in solution in the official method causing an unsatisfactory solochrome end-point and, possibly, slightly high results. If precipitated bismuth oxychloride remains in the titration liquid after addition of EDTA it is slowly soluble, resulting in erroneous results unless the titration is carried out rapidly after addition of the complexing agent. The detailed methods are followed by a suggested scheme of separation.

Method I

The determination of Aluminium in the presence of Bismuth

To a quantity of solution believed to contain sufficient bismuth and aluminium to react with about 12 ml. of the complexing solution add 25 ml. of 0·1N EDTA and 80 ml. of water and proceed by the method described for the determination of aluminium, commencing with the words "neutralise to congo red paper. . . ." From the quantity of EDTA used subtract the amount required to titrate the bismuth in the same volume of solution using the catechol violet method; each ml. of 0·1N EDTA is equivalent to 0·001349 g. of Al.

NOTE: If too large an excess of EDTA is added, precipitation of bismuth-EDTA complex may occur causing an unsatisfactory end-point. If too small an amount is added there will be a danger that the aluminium will be incompletely complexed.

Using the above conditions, satisfactory recoveries of aluminium in the presence of bismuth were obtained.

Method II

The determination of Magnesium or Calcium in the presence of Bismuth

To a suitable aliquot of the slightly acid solution containing bismuth and magnesium or calcium, add 25 ml. of 0·1N EDTA, 100 ml. of water

and a few drops of solochrome black indicator; add dilute solution of ammonium hydroxide drop by drop until just blue, and then 1 ml. in excess; add more indicator as required and titrate with 0·1N calcium chloride. From the quantity of EDTA used subtract the amount required to titrate the bismuth in the same volume of solution using the catechol violet method; each ml. of 0·1N EDTA used is equivalent to 0·001216 g. of Mg. (or 0·002004 g. of Ca).

NOTES: 1. If only bismuth and calcium are being determined a little magnesium-EDTA complex should be added to the solution to sharpen the end-point.

2. It is important that the amount of ammonia added should not exceed that stated; at higher *p*H values the full blue colour of the indicator does not develop satisfactorily, a reddish-blue colour being obtained which seriously masks the end-point.

Some results obtained by this method are included in Table VI.

TABLE VI

DETERMINATION OF A STANDARD MAGNESIUM* SOLUTION BY EDTA TITRATION

	g. of Mg per litre
1. No other metals present	1·509
2. By method IV, but without added Al	1·508
3. By method IV, fivefold equivalent of Al present	1·504
„ „ „	1·510
„ „ „	1·509
4. By method IV, 2 minutes standing	1·510
5. „ „ „ 5 „ „	1·520
6. „ „ „ 10 „ „	1·535
7. „ „ „ 15 „ „	1·549
8. „ „ „ 30 „ „	1·600
9. By method II, one equivalent of Bi present	1·511
10. „ „ „ two equivalents „ „	1·509
11. „ „ „ three „ „ „	1·505
12. By method III, three equivalents of Bi removed	1·509

* The magnesium was first determined as pyrophosphate[21] and, in duplicate determinations, the solution was found to contain 1·507 g. and 1·511 g. of Mg per litre.

Method III

The removal of Bismuth prior to the determination of Magnesium and Calcium

To a suitable aliquot containing sufficient calcium and magnesium for the determination of each metal, add 2 ml. of dilute hydrochloric acid, 150 ml. of water and sufficient dilute solution of ammonia until the mixture is only just acid to litmus paper; heat to boiling and boil for 2 minutes, stirring to prevent bumping; cool in ice, confirm that precipitation is complete by the addition of a few drops of brine and filter through a No. 42 Whatman filter paper, washing with cold water; adjust the combined filtrate and washings to a suitable volume with water.

To one aliquot add 10 drops of solution of potassium cyanide, 10 ml. of ammonia buffer solution and sufficient solochrome black indicator, and titrate with 0·1N EDTA to give the combined titre for calcium and magnesium.

To a second aliquot add 25 ml. of 0·1N EDTA, 5 ml. of solution of sodium hydroxide and 0·2 g. of murexide indicator, and titrate the excess of EDTA with 0·1N calcium chloride to give the titre for calcium.

NOTE: The solochrome black end-point is considerably improved by the addition of the cyanide, which serves to complex any trace of heavy metals left in solution.

Some results obtained for a magnesium solution by this method are included in Table VI.

Method IV

The determination of Magnesium or Calcium in the presence of Aluminium

To a suitable aliquot of the slightly acid solution containing aluminium and magnesium (or calcium) add 1 g. of ammonium chloride, sufficient solution of triethanolamine so that the precipitate which at first forms completely redissolves (about 25 to 40 ml.) 200 ml. of water, 5 ml. of ammonia buffer solution and sufficient solochrome black indicator to give a full red colour; titrate immediately with 0·1N EDTA to the formation of a full blue colour; each ml. of 0·1N EDTA is equivalent to 0·001216 g. of Mg (or 0·002004 g. of Ca).

NOTES: 1. The red colour changes to purple about ½ to 1 ml. before the end-point and thus provides a useful indication that the end-point is near.

2. Whilst it is agreed that the blue end-point fades back to purple on standing, no difficulty with fading before the end-point, as has been found by Ritchie[20], has ever been encountered using the above procedure. He suggests that the titration be carried out at a temperature below 5° C., but at the dilution used in the proposed method this modification would appear to be unnecessary.

On carrying out a number of determinations by the procedure described it was observed that high results were obtained if solutions were allowed to stand before titration, probably due to a gradual hydrolysis of the aluminium-triethanolamine complex. A standard magnesium solution was therefore prepared and a number of determinations were made to find the rate and extent of the breakdown under the conditions stated. Some determinations of the magnesium in the presence of bismuth, both by the titration of the two metals together (Method II) and the separation procedure (Method III) were also made. The results are listed together in Table VI.

It is obvious from results 3 to 8 that Method IV is only satisfactory if the titration is carried out as soon as possible after addition of the triethanolamine and dilution with water.

Method V

The determination of Magnesium and Calcium in the presence of Aluminium

The magnesium and calcium are determined together using Method IV. The calcium is then determined as follows:—

To a suitable aliquot of the slightly acid solution containing aluminium, calcium and magnesium add sufficient solution of triethanolamine followed by 5 ml. of N sodium hydroxide; if a gelatinous precipitate forms at this stage filter off and wash the filter with water, collecting about 200 ml. of combined filtrate and washings; if no precipitate forms, dilute with water

to 200 ml.; to the resulting solution add 0·2 g. of murexide indicator and titrate with 0·1N EDTA; each ml. of 0·1N EDTA is equivalent to 0·002004 g. of Ca.

NOTE: The end-point in this determination is not as well-defined as others described in this work, but is quite satisfactory for routine application.

These methods are classified below into a scheme for dealing with mixtures.

Section I. Bi present

Titrate Bi by Catechol Violet method and then proceed as described below according to the other metals present.

A. If Al is present. Titrate Bi and Al together by Method I; on another portion of solution precipitate Bi and most of the Al by Method III, and determine Mg and/or Ca by Methods IV and V.

B. If Al is absent. If either Mg or Ca is present, determine together with Bi by Method IV; if both Mg and Ca are present, remove Bi and determine Mg and Ca by Method III.

Section II. Bi absent

A. If Al is present. Titrate Al by the thorium nitrate method; determine Mg and/or Ca by Methods IV and V.

B. If Al is absent. Titrate Mg and Ca by the solochrome black method; titrate Ca by the murexide method.

APPLICATION OF THE METHODS TO SOME TYPICAL PHARMACEUTICAL PRODUCTS

1. *Materials containing Bismuth*

Unless otherwise directed in the footnotes, the general method to be adopted is as follows:—

Dissolve the stated amount of material in a sufficient quantity of dilute nitric acid to give a clear solution when diluted to 50 ml. and proceed by the method described for the determination of bismuth, commencing with the words "add 2 drops of catechol violet indicator. . . ."

Table VII shows the application of this procedure to the determination of bismuth in various pharmaceutical materials.

Some examples are now given in which bismuth is associated with other metals mentioned in the scheme to demonstrate the general method of application.

Mixture of bismuth, N.F. 1939. Assay for bismuth. Dissolve 10 ml. in just sufficient nitric acid to give a clear solution when diluted to 50 ml. with water and proceed by the method described for the determination of bismuth commencing with the words "add 2 drops of catechol violet indicator. . . ." Assay for magnesium. Dissolve 10 ml. in nitric acid and dilute to exactly 50 ml. with water; take 5 ml. of the dilution and proceed by Method II, subtracting from the volume of 0·1N EDTA used one tenth of the volume required in the determination of bismuth. Results obtained are shown in Table VIII.

TABLE VII

THE DETERMINATION OF BISMUTH IN VARIOUS PHARMACEUTICAL MATERIALS

Product	Amount taken for determination	See footnote	Result (per cent. Bi) By EDTA	Result (per cent. Bi) By reference method
Bismuth Carbonate, B.P.	0·2 g.		80·9	81·4 (Ignition)
Bismuth Citrate, B.P.C. 1949	0·3 g.		51·9	52·4 (Ignition)
Bismuth Oxyiodide	0·35 g.	(*a*)	56·7	57·0 (Phosphate)
Bismuth Precipitated, B.P.	0·2 g.			
Bismuth Salicylate, B.P.	0·3 g.		57·4	57·3 (Ignition)
Bismuth Sodium Tartrate, B.P.	0·4 g.		40·7	40·7 (Phosphate)
Bismuth Subgallate, B.P.	0·3 g.	(*b*)	47·1	47·4 (Ignition)
Bismuth Subnitrate, B.P.C.	0·25 g.		72·9	73·4 (Ignition)
Bismuth Tribromphenate, B.P.C. 1949	0·35 g.	(*c*)	52·6	52·9 (Phosphate)
Injection of Bismuth, B.P.	Equivalent of 0·2 g. Bi	(*d*)		
Injection of Bismuth Salicylate, B.P.C.	5 ml.	(*e*)		
Mixture of Bismuth with Pepsin, Compound, B.P.C. 1934	5 ml.	(*f*)	5·08	5·09 (Phosphate)
Ointment of Resorcinol Compound, B.P.C.	6 g.	(*g*)	5·71	5·80 (B.P.C. method)
Paste of Bismuth Subnitrate and Iodoform, B.P.C.	1 g.	(*h*)	18·3	18·4 (B.P.C. method)
Solution of Bismuth and Ammonium Citrate, B.P.C. 1949	20 ml.	(*i*)	4·65	4·64 (Phosphate)
Solution of Bismuth, Concentrated, B.P.C. 1949	10 ml.	(*i*)	9·42	9·42 (Ignition)

(*a*) Treat with excess of nitric acid and heat to dryness on a water bath, repeating if necessary until all iodine is expelled. Dissolve the residue in the minimum amount of dilute nitric acid and proceed by the general method.

(*b*) Gently ignite at a temperature not exceeding 500° C., cool, dissolve the residue in the minimum quantity of warm nitric acid and proceed by the general method.

(*c*) Add 10 ml. of dilute nitric acid to the sample, keeping the mixture cool to prevent nitration; shake with 10 ml. of ether, separate and wash the ether with 2 portions, each of 5 ml. of dilute nitric acid; combine the acid fractions, dilute to 50 ml. with water acidified with nitric acid if necessary and proceed by the general method.

(*d*) Prepare a solution as described in the assay of the B.P. and use an accurately measured volume, equivalent to about 0·2 g. of bismuth for determination by the general method.

(*e*) Prepare a solution as described in the assay of the B.P.C. and continue the determination by the general method instead of precipitating bismuth as phosphate.

(*f*) Evaporate to dryness, ignite at a temperature not exceeding 500° C., dissolve the residue in the minimum amount of nitric acid, dilute to 50 ml. and proceed by the general method.

(*g*) Destroy the fat by gentle ignition, then continue the ignition at a temperature not exceeding 500° C.; dissolve the residue in nitric acid and dilute to 50 ml. To 20 ml. of this solution add 30 ml. of water and more nitric acid if necessary to maintain a clear solution, and proceed by the general method.

NOTE: The zinc has also been determined successfully in this preparation by treating 10 ml. of the solution obtained in the assay for bismuth by Method II or Method III. If Method III is used the addition of cyanide must, of course, be omitted.

(*h*) Digest with warm chloroform, filter, wash the residue with warm chloroform until the washings are free from iodoform and fat, dissolve the residue in the minimum amount of nitric acid and proceed by the general method.

(*i*) Dilute to 100 ml. and titrate 20 ml. of the dilution by the general method.

Compound lozenges of bismuth, B.P.C. Assay for bismuth. Take a sample of 20 lozenges and determine the average weight. Powder the sample and ignite an accurately weighed quantity of the powder, equivalent to about 4 lozenges, at a temperature not exceeding 500° C.; cool, moisten the residue with water, dissolve in the minimum quantity of nitric acid and dilute to 100 ml. with 0·1N nitric acid. Dilute 30 ml. to 50 ml. with water and proceed by the method described for the determination of bismuth commencing with the words "add 2 drops of catechol violet

TABLE VIII

THE DETERMINATION OF BISMUTH AND MAGNESIUM IN MIXTURE OF BISMUTH

Sample No.	Per cent.	By EDTA	By classical gravimetric separation
I	Bi	1·81	1·79
	Mg	1·28	1·29
II	Bi	1·83	1·84
	Mg	1·17	1·19

indicator . . ."; each ml. of 0·1N EDTA is equivalent to 0·01045 g. of Bi. Calculate the proportion of Bi in each lozenge of average weight.

Assay for calcium carbonate. To 10 ml. of the solution prepared in the assay for bismuth add 2 ml. of dilute hydrochloric acid, 150 ml. of distilled water and make just acid to litmus paper by using dilute solution of ammonia and dilute hydrochloric acid; heat to boiling and boil for 2 minutes, stirring to prevent bumping; cool in ice, confirm that precipitation is complete by addition of a few drops of brine, and filter through a No. 42 Whatman filter paper; wash with cold water and adjust the volume of the combined filtrate and washings to 250 ml. with water; to 100 ml. of this solution add 25 ml. of 0·1N EDTA, 5 ml. of solution of sodium hydroxide, 10 drops of solution of potassium cyanide and 0·2 g. of murexide indicator and titrate with 0·1N calcium chloride; each ml. of 0·1N EDTA is equivalent to 0·005004 g. of $CaCO_3$. Calculate the proportion of $CaCO_3$ in each lozenge of average weight. Assay for magnesium. To a further 100 ml. of the solution prepared in the assay for calcium carbonate add 10 ml. of ammonia buffer solution, 10 drops of solution of potassium cyanide and sufficient solochrome black indicator and titrate with 0·1N EDTA; each ml. of 0·1N EDTA, after the volume required in the determination of calcium carbonate has been deducted, is equivalent to 0·001216 g. of Mg. Calculate the proportion of Mg in each lozenge of average weight. Results obtained by this method are shown in Table IX.

Compound Powder of Bismuth, B.P.C., is clearly determinable by the same procedure, except that there is no necessity to ignite.

TABLE IX

THE DETERMINATION OF BISMUTH, CALCIUM AND MAGNESIUM IN COMPOUND LOZENGES OF BISMUTH, B.P.C.

	By proposed method	By B.P.C. 1954 method
Content of	g. per lozenge	g. per lozenge
Bi	0·127	0·126
$CaCO_3$	0·312	0·312
Mg	0·041	0·041

2. *Materials containing Aluminium*

The general method to be adopted is as follows:—

Dissolve the stated amount of material in just sufficient hydrochloric acid and dilute to 100 ml. with water. To 10 ml. of the solution add 25 ml. of 0·1N EDTA and 80 ml. of water and proceed by the method described for the determination of aluminium, commencing with the words "neutralise to congo red paper. . . ."

Table X shows the application of this method to the determination of aluminium in various pharmaceutical materials.

An example of application of the method to a mixture of aluminium and magnesium is provided by a proprietary product consisting of a suspension containing approximately 4 per cent. of Al_2O_3 and 1·2 per cent. of MgO. The method adopted was as follows:—

Dissolve 15 ml. of the mixture in a slight excess of dilute hydrochloric acid and dilute to 250 ml. with water.

Assay for aluminium. To 10 ml. of the dilution add 25 ml. of 0·1N EDTA and 80 ml. of water and proceed by the method described for the determination of aluminium, commencing with the words "neutralise to congo red paper. . . ."

TABLE X

THE DETERMINATION OF ALUMINIUM IN VARIOUS PHARMACEUTICAL MATERIALS

Product	Amount taken for determination (g.)	Result (per cent. Al_2O_3)	
		By EDTA	By reference method
Aluminium Hydroxide Gel, B.P.C.	0·6	50·3	50·0 (B.P.C. method)
Aluminium Hydroxide Gel, B.P.C.	7	3·76	3·80 (,, ,,)
Aluminium Hydroxide Paste, Concentrated (containing approximately 6 to 7 per cent. Al_2O_3)	4	7·53	7·46 (Oxine)
		7·43	7·47 ,,
		5·81	5·81 ,,
		6·59	6·65 ,,
		7·34	7·28 ,,

Assay for magnesium. To 50 ml. of the dilution add 1 g. of ammonium chloride, and proceed by Method IV commencing with the words "sufficient solution of triethanolamine. . . ."

Results obtained using this method are shown in Table XI.

TABLE XI

THE DETERMINATION OF ALUMINIUM AND MAGNESIUM IN A SUSPENSION OF THE MIXED HYDROXIDES

Sample No.	Aluminium (per cent. Al_2O_3)		Magnesium (per cent. MgO)	
	By EDTA	By hydroxide precipitation	By EDTA (Al masked)	By EDTA (Al removed)
1	4·05	4·08	1·26	1·27
2	3·92	3·98	1·29	1·30
3	4·10	4·06	1·21	1·20
4	4·06	4·04	1·19	1·19
5	3·88	3·97	1·27	1·27

One final example of separations using this scheme is that of a digestive powder containing aluminium hydroxide, magnesium trisilicate, magnesium oxide and about 4 per cent. of vegetable powders. This was assayed by first removing the silica by the gravimetric method described for magnesium trisilicate in the British Pharmacopœia, followed by determinations of aluminium and magnesium in the resulting solution. The quantity of vegetable material present was not sufficient to warrant its removal, but should interference be encountered the sample may be ignited as a preliminary measure.

APPENDIX

Reagents used throughout this work

For convenience the reagents used in the various determinations are listed below in alphabetical order. Where water is mentioned it is intended that distilled or deionised water be used.

Alizarin S indicator: 0·1 per cent. w/v of alizarin S in water.

Ammonia buffer solution: dissolve 13·5 g. of reagent grade ammonium chloride in 114 ml. of strong solution of ammonia and dilute to 200 ml. with water.

NOTE: This preparation is not the ammonia buffer solution of the B.P.C., which contains magnesium-EDTA complex.

Ammonia, dilute solution of: of the B.P.

Calcium chloride, 0·1N: a solution of hydrated calcium chloride in water, containing 10·96 g. of $CaCl_2,6H_2O$ per litre.

This solution is conveniently standardised by titration with 0·1N EDTA using solochrome black indicator.

Catechol violet indicator: 0·1 per cent. w/v of catechol violet in water.

EDTA, 0·1N: a solution of the disodium salt of ethylenediaminetetra-acetic acid in water, containing 18·61 g. of $C_{10}H_{14}O_8N_2Na_2,2H_2O$ per litre.

Standardise by titration of pure zinc metal according to the following procedure:—

Dissolve about 0·7 g., accurately weighed, of pure zinc metal in the minimum quantity of dilute hydrochloric acid and dilute to 250 ml. with water. Take 25 ml., dilute to 150 ml. with water, add 10 ml. of ammonia buffer solution, sufficient solochrome black indicator and titrate with the 0·1N EDTA to be standardised.

NOTE: It is important that, for general application to the methods described, the standard disodium ethylenediaminetetra-acetate solution of the B.P.C. should not be used. The latter solution, intended for the titration of calcium and magnesium only, contains a proportion of magnesium which would remain complexed under the conditions of standardisation given above, and during titrations in alkaline media. For the acid titrations of aluminium and bismuth, however, additional EDTA would be released from the magnesium-EDTA complex and the factor would be correspondingly low.

Hydrochloric acid, dilute: of the B.P.

Monochloroacetic acid, 2M: a solution of monochloroacetic acid in water, containing 189 g. of $CH_2Cl{\cdot}COOH$ per litre.

Murexide indicator: of the B.P.C. Appendix IV.

Nitric acid, dilute: of the B.P. Appendix I.

Potassium cyanide, solution of: of the B.P. Appendix I.

Sodium acetate, 1M: a solution of sodium acetate in water, containing 136 g. of $CH_3COONa,3H_2O$ per litre.

Sodium hydroxide, solution of: of the B.P. Appendix I.

Solochrome black indicator: a freshly prepared 0·5 per cent. solution of solochrome black in ethanol (95 per cent.).

In the opinion of the authors this freshly prepared solution is far superior to the various "stabilised" solutions, or to the salt diluted indicator of the B.P.C. The solution provides a very sharp end-point indicator up to a period of about 3 hours from the time of preparation.

Thorium nitrate, 0·1N: a solution of thorium nitrate in water, containing 27·6 g. of $Th(NO_3)_4,4H_2O$ per litre.

This solution is conveniently standardised by titration of standard EDTA using the conditions described for the determination of aluminium.

Triethanolamine, solution of: a 30 per cent. v/v solution of triethanolamine in water. For application to the macro-scale work described above, triethanolamine of B.P.C. quality has been found to be perfectly satisfactory.

With the exception of Solochrome Black Indicator all the above reagents have been found to be stable over a period of several months. 1M Sodium Acetate readily supports mould growth, but in the authors' experience this has had no effect on its buffering capacity. The mould growth may be suppressed, however, by preparation of the reagent with chloroform water.

Summary

1. Published methods for the volumetric determinations of aluminium and of bismuth with EDTA have been examined. The effect of variation of conditions of reaction on the accuracy of the determination of aluminium by back-titration with thorium nitrate has been investigated. Modifications to the procedure for the determination of bismuth using catechol violet as indicator have been proposed.

2. Methods of determining aluminium, bismuth, calcium and magnesium in the presence of each other have been described.

3. Examples have been given of applications of the methods to a number of commonly occurring pharmaceutical products to demonstrate their general applicability.

We wish to express our thanks to Mr. C. Vickers, for much of the experimental work and for the valuable suggestions he has made throughout.

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DISCUSSION

The paper was presented by MR. H. E. BROOKES.

DR. G. E. FOSTER (Dartford) said one minor criticism he wished to make was that the abbreviation "EDTA" had been used extensively, but at different times referred to the acid itself, the disodium salt and the tetra-sodium salt.

DR. D. C. GARRATT (Nottingham) hoped others would present papers in the future describing rapid methods of assay which were sufficiently accurate provided their limitations were realised.

MR. H. D. C. RAPSON (Dorking) said his colleague, Mrs. Mary Taylor, had altered her technique in respect of the aluminium determination to bring it very much in line with the method described in the paper.

DR. G. BROWNLEE (London) explained the difficulty in printing long chemical names which were repeated many times in a paper. It was the accepted practice in such cases for the author to use an abbreviation provided he explained its meaning properly, which in this case was so.

MR. C. A. JOHNSON, in reply, said that the only question raised had been answered by Dr. Brownlee.