New Indicator for the Complexometric Titration of Calcium with EDTA

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A new indicator, hydroxy naphthol blue, A.R., has been evaluated for the complexometric titration of calcium. Procedures are presented for the determination of calcium salts, dosage forms containing calcium, and for mixtures of calcium and magnesium. The methods are simple, accurate, and more rapid than the conventional oxalate procedures.

THE USE OF EDTA for complexometric titrimetry was first described by Schwarzenbach *et al.* in 1946 (1). The same procedure was used by Mattocks and Hernandez (2) for the determination of calcium products and by Griffenhagen *et al.* (3) for the assay of tablets containing calcium salts.

When both calcium and magnesium are present, the conditions for the titration are usually based upon the titration of the total calcium and magnesium, in an ammoniacal buffer, with EDTA using Eriochrome Black T as the indicator, followed by the determination of the calcium in a second sample after precipitation of the magnesium as the hydroxide and using murexide as the indicator (4, 5). Other investigators have recommended the separation of calcium from the mixture as the oxalate (6–9). The separation of the mixture by ion exchange has also been advocated (10, 11). More recently, the direct titration of calcium in the presence of magnesium has been achieved by employing a titrant which complexes the calcium selectively (12) or by using an indicator specific for calcium (13–15).

In the present paper, procedures are presented for the analysis of calcium salts and for dosage forms containing calcium by titration with EDTA using a new indicator, hydroxy naphthol blue,[1] A.R., which is specific for calcium. Procedures are also given for the determination of calcium in the presence of magnesium which eliminates separation of the two elements by using an indicator which complexes the calcium selectively.

EXPERIMENTAL

Reagents.—Standard EDTA solution, 0.05 *M;* potassium hydroxide solution, 1 *N;* hydroxy naphthol blue indicator, A.R.; Calmagite indicator,[2] A.R.; and ammonia buffer, prepared by dissolving 67.5 Gm. of ammonium chloride and 570 ml. of ammonium hydroxide, A.R., in sufficient water to make 1 L.

Analysis of Calcium Salts.—An amount of the dried calcium salt equivalent to 30–40 mg. of calcium, was weighed accurately into a 250-ml. flask and dissolved in water. If the sample was not water soluble, sufficient 10% hydrochloric acid was added until solution was effected. The mixture was diluted to 150 ml., the solution adjusted to pH 12–12.5 with 1 *N* potassium hydroxide (about 15 ml.), and the sample titrated with 0.05 *M* EDTA using 0.2–0.3 Gm. of hydroxy naphthol blue indicator. The end point color change was from pink to deep blue. Each milliliter of EDTA titrant is equivalent to 2.004 mg. of calcium. The results obtained are presented in Table I.

Analysis of Dosage Forms.—The proposed procedure was applied to tablets and injections containing calcium. Calcium chloride and calcium gluconate injections were analyzed by pipeting aliquots of the solution equivalent to 30–40 mg. of calcium into a 250-ml. flask; the calcium was titrated as described under *Analysis of Calcium Salts.*

For the analysis of the calcium salts in tablets, 20 tablets were weighed and finely powdered. An amount of the calcium mixture, equivalent to 200–250 mg. of calcium, was weighed and dissolved in water with the aid of 10% hydrochloric acid, and sufficient water was added to make 100 ml. An aliquot of this solution, representing 30–40 mg. of calcium, was then taken for analysis. The results are reported in Table II.

Analysis of Mixtures of Calcium and Magnesium.—Several mixtures containing varying amounts of calcium carbonate and magnesium oxide were analyzed by direct titration with EDTA.

Total Calcium and Magnesium.—An amount of the powdered mixture, equivalent to 0.5 Gm. of calcium carbonate, was weighed accurately and dissolved in water using sufficient 10% hydrochloric acid to effect solution; the mixture was diluted to 100 ml. in a volumetric flask.

Appropriate aliquots of the solution were pipeted into a 250-ml. flask, the solution adjusted to pH 10 with ammonia buffer (about 5 ml.), and the sample titrated with 0.05 *M* EDTA using 0.1 Gm. of Calmagite indicator. The end point color change was from wine-red to blue. Each milliliter of 0.05 *M* EDTA is equivalent to 2.004 mg. of calcium and 1.216 mg. of magnesium.

Calcium.—A second aliquot of the solution was pipeted into a 250-ml. flask, the solution adjusted to pH 12–12.5 with 1 *N* potassium hydroxide

TABLE I.—ANALYSIS OF CALCIUM SALTS

Calcium Salt	Taken, mg.	Found, mg.	Recovery, %
Calcium acetate	150	149.7	99.8 ± 0.12[a]
Calcium bromide[b]	150	140.9	93.9 ± 0.18
Calcium carbonate	100	99.8	99.8 ± 0.20
Calcium chloride	100	100.5	100.5 ± 0.20
Calcium gluconate	250	250.4	100.2 ± 0.15
Calcium hydroxide	50	49.9	99.8 ± 0.22
Calcium lactate	150	149.7	99.8 ± 0.13

[a] Average of four determinations ± standard deviation.
[b] The hygroscopic nature of calcium bromide resulted in a low percentage recovery.

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[1] Hydroxy Naphthol Blue Indicator, A.R., Mallinckrodt Chemical Works, St. Louis, Mo.

[2] Calmagite Indicator, A.R., Mallinckrodt Chemical Works, St. Louis, Mo.

TABLE II.—ANALYSIS OF DOSAGE FORMS CONTAINING CALCIUM

Dosage Form	Calcium Salt	Labeled Amt.	Recovery, %
Injection[a]	Calcium chloride	100 mg./ml.	102.5 ± 0.30[b]
Injection	Calcium gluconate	100 mg./ml.	110.9 ± 0.10
Tablet	Calcium carbonate	0.65 Gm./tablet	96.9 ± 0.27
Tablet	Calcium gluconate	1.0 Gm./tablet	97.9 ± 0.23
Tablet	Calcium lactate	0.65 Gm./tablet	99.7 ± 0.18
Tablet, antacid	Calcium carbonate	0.42 Gm./tablet	95.0 ± 0.40

[a] The calcium chloride injection used for this analysis was buffered with calcium hydroxide. [b] Average of four determinations ± standard deviation.

TABLE III.—ANALYSIS OF MIXTURES OF CALCIUM CARBONATE AND MAGNESIUM OXIDE

	Calcium Carbonate			Magnesium Oxide		
$CaCO_3$/MgO Wt. Ratio	Taken, mg.	Found, mg.	Recovery, %	Taken, mg.	Found, mg.	Recovery, %
90/10	75	75.80	101 ± 0.30[a]	8.33	8.27	99.3 ± 0.11[a]
80/20	75	75.30	100.4 ± 0.25	18.75	18.51	98.7 ± 0.12
70/30	75	75.21	100.3 ± 0.12	21.43	21.31	99.4 ± 0.12
60/40	75	75.45	100.6 ± 0.23	33.33	33.13	99.4 ± 0.13
50/50	75	75.58	100.8 ± 0.12	25.00	24.91	99.6 ± 0.11
40/60	75	75.45	100.6 ± 0.10	37.50	37.05	98.8 ± 0.28
30/70	75	76.07	101.4 ± 0.12	35.00	34.29	98.0 ± 0.12
20/80	75	75.57	100.7 ± 0.31	40.00	39.29	98.2 ± 0.11

[a] Average of four determinations ± standard deviation.

and the sample titrated with 0.05 *M* EDTA using 0.2 Gm. of hydroxy naphthol blue indicator.

Magnesium.—The concentration of magnesium in the sample was calculated by subtracting the volume of EDTA used for the calcium titration from the volume used in the total calcium and magnesium titration.

The results obtained by these procedures are presented in Table III.

The volumetric determination of calcium by titration with EDTA is accurate and more rapid and convenient than the traditional oxalate method. The procedure has been demonstrated to be applicable readily to the analysis of pharmaceutical dosage forms containing calcium. A new indicator, hydroxy naphthol blue, has been shown to be suitable for analysis of calcium by the EDTA procedure and to be applicable for the determination of calcium in the presence of magnesium. In the titration of mixtures of calcium carbonate and magnesium oxide, the end point was detected readily until the ratio of magnesium to calcium became excessively high, at which point the magnesium hydroxide precipitate rendered detection of the end point difficult.

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ERRATUM

In the article titled "Kinetic Analysis of Blood Levels and Urinary Excretion in the Absorptive Phase after Single Doses of Drug" (1), the following correction should be made on page 1401:

The constant, K, in the denominator of the first term on the right-hand side of Eq. 14A should be removed.

(1) Wagner, J. G., and Nelson, E., THIS JOURNAL, **53**, 1392 (1964).