

Improved Assay for Dibasic Calcium Phosphate

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Phosphate ion interference in chelometric titration of calcium can be eliminated by extracting the anion as phosphomolybdic acid. A titrimetric procedure for calcium ion in dibasic calcium phosphate is described. Thermogravimetric analysis shows that dibasic calcium phosphate dihydrate is thermally stable to at least 80°, obviating conversion to the pyrophosphate before assay. The proposed procedure has advantages of speed and accuracy over the U.S.P. assay.

DIBASIC CALCIUM phosphate is an important raw material used in medicine as a calcium replenisher. It has extensive use in pharmacy as an excipient, where it is especially valuable in tablets made by direct compression. Although the official compendia have adopted chelometric titrations for assay of most calcium salts (1), the classical oxalate precipitation and permanganate titration were retained in U.S.P. XVII (2) for dibasic calcium phosphate because phosphate ion interferes with the direct titration of calcium. A procedure which circumvents this interference is reported here.

Assay of dibasic calcium phosphate by the U.S.P. method was found cumbersome and slow in these laboratories, and the values obtained were biased at the low end of the specification. Ion-exchange separation of calcium and phosphate (3) proved unsatisfactory due to incomplete elution of calcium from the resin. Phosphate can be assayed gravimetrically as magnesium pyrophosphate (4), but that procedure has no advantage over the present U.S.P. assay.

Solvent extraction of phosphate as phosphomolybdic acid (5, 6) removes the interference to chelometric titration of calcium, and the yellow color of the extract affords a means for quantitative spectrophotometric determination of phosphate ion as well as obviating an identification test for phosphate. Although quantitation of both the cation and anion are possible, titration of the calcium suffices for quality control of the salt.

In the U.S.P. assay, the salt is dried at 80–850°, and results are reported on the dried basis. In employing this procedure one can omit the drying step because thermogravimetric analysis indicates (a) dihydrate is stable to at least 80° and (b) samples showed about 1% or less moisture. However, the addition of a simple "loss on drying" or a thermogravimetric determination

can provide the data necessary for obtaining an accuracy of better than 1%.

EXPERIMENTAL

Materials and Supplies—Dibasic calcium phosphate dihydrate U.S.P., hydroxy naphthol blue indicator (U.S.P. XVII, p. 1068), concentrated, 10%, and 1 *N* hydrochloric acid, 40% sodium molybdate, "mixed solvent" (1:1 *n*-butanol-chloroform), 10% sodium hydroxide, exsiccated sodium phosphate N.F., 0.05 *M* disodium ethylenediaminetetraacetate (EDTA), a Beckman DU spectrophotometer, a duPont Thermogravimetric analyzer, model 950, and standard laboratory glassware were used in this work.

Determination of Calcium—Accurately weigh about 1000 mg. of dibasic calcium phosphate dihydrate,¹ and transfer it to a 100-ml. volumetric flask. Add 30 ml. of 10% hydrochloric acid to dissolve the salt, and dilute the solution to the mark with water. Transfer a 5.0-ml. aliquot of the solution to a 250-ml. separator containing 20 ml. of water, 3 ml. of 40% sodium molybdate, and 2 ml. of concentrated hydrochloric acid. Extract the yellow phosphomolybdic acid with three 20-ml. vols. of mixed solvent. Wash the combined extracts with 10 ml. of 1 *N* hydrochloric acid, and add the washings to the aqueous layer.

Adjust the pH of the aqueous layer to 12.5 by adding about 20 ml. of 10% sodium hydroxide. Add 300 mg. of hydroxy naphthol blue indicator, and titrate the violet solution to a persistent blue end point with standard 0.05 *M* EDTA.

$$\% \text{CaHPO}_4 \cdot 2\text{H}_2\text{O} =$$

$$V \times M \times 172.09 \times 100/5 \times 100/\text{mg. sample}$$

where *V* = volume of titrant used, and *M* = molarity of titrant.

Thermogravimetric Analysis—Samples were heated at rates and spans described in Figs. 1 and 2.

RESULTS

Comparison with U.S.P. Assay—Two lots of dibasic calcium phosphate dihydrate were assayed by the proposed and U.S.P. procedures by two different analysts on different days. The results are presented in Table I.

No interference from chlorides, alkali metal cations, or fluoride was encountered in the chelometric assay of dibasic calcium phosphate in a formulation.

¹ Compensate for weight of water which can be expeditiously removed by drying for 3 hr. at 60° *in vacuo*.

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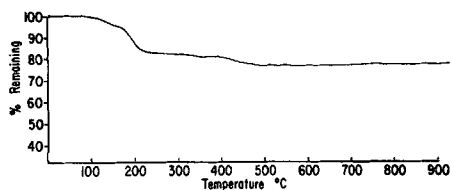


Fig. 1—Thermogram of dibasic calcium phosphate dihydrate U.S.P. over a 900° range. A loss in weight of sample is not noted until a temperature close to 100° is reached. The sample then continues to lose weight up to 500°, at which point no further loss is evident. The per cent remaining was measured as 78, which corresponds to the percentage of anhydrous calcium phosphate present in the dihydrate salt. The equipment was operated at a rate of 25° per minute.

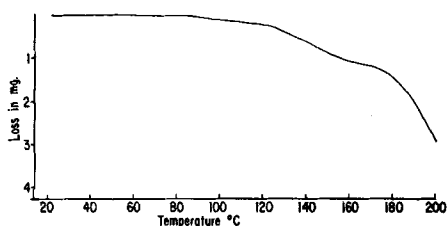


Fig. 2—Similar to Fig. 1, except that the temperature scale was expanded over the 0-200° span at a rate of 20° per minute. This thermogram indicates no loss in weight of sample below 82°.

SUMMARY AND CONCLUSIONS

1. A chelometric titration procedure for dibasic calcium phosphate has been described which compares favorably with the U.S.P. assay in simplicity, speed, and accuracy.

2. Extraction of phosphate as phosphomolybdic acid by an *n*-butanol-chloroform (1:1) mixture eliminates the interference of the anion in the titration of the calcium ion and obviates identification test B in the U.S.P. monograph for the salt.

3. Thermogravimetric analysis of samples indicated that the dihydrate is stable to at least 80° and their moisture content was 1% or less, thus justifying the elimination of the drying step which is required in the U.S.P. method. Furthermore, ignition of sample converts the salt to the pyrophosphate which would obviate the use of the proposed procedure.

4. A thermogravimetric determination of free moisture content provides the correction factor for obtaining accuracy of better than 1%. Alter-

TABLE I—COMPARISON OF PROPOSED AND U.S.P. CALCIUM ASSAYS

Lot	Analyst	U.S.P.	% CaHPO ₄ ·2H ₂ O	
			Proposed Method—As Is	Anhydrous ^a
A	1	98.3 98.2	99.5	100.5
			99.8	100.8
			99.8	100.8
			100.2	101.2
			98.6	99.6
			99.5	100.5
B	2	96.0	99.8	100.8
			99.3	100.3
			99.0	100.0
			99.0	100.0
			99.8	100.8
			99.8	100.3
C	3	98.6	100.0	100.5
			100.0	100.5
			100.3	100.8
			100.9	101.4
			98.9	99.4
			99.5	100.0
D	3	99.0 97.8	100.0	100.5
			100.0	100.5
			100.2	100.7
			100.2	...
			99.1	...
			99.8	...
As is			Anhydrous	
Av. Lot A =	99.5 ± 0.56 (S.D.)	100.5 ± 0.56		
Lot B =	100.0 ± 0.63 (S.D.)	100.5 ± 0.63		

^a Moisture determined by thermogravimetry. (See Table II.)

TABLE II—COMPARISON OF MOISTURE DETERMINATION BY LOSS ON DRYING (LOD) (60° FOR 3 hr. UNDER VACUUM) AND THERMOGRAVIMETRIC ANALYSIS (TGA)

Lot	LOD, %	TGA, %
A	0.93	1.09
B	0.62	0.51

natively, a loss on drying technique (see Table II), although not as accurate, gives a reasonable indication of free moisture present.

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