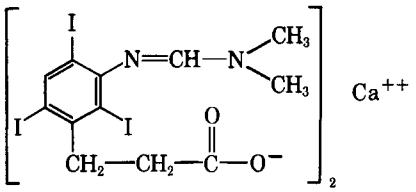
Qualitative and Quantitative Tests for Calcium Ipodate

Provisional, unofficial monographs are developed by the Drug Standards Laboratory, in cooperation with the manufacturers of the drug concerned, for publication in the *Journal of Pharmaceutical Sciences*. The ready availability of this information affords discriminating medical and pharmaceutical practitioners with an added basis for confidence in the quality of new drug products generally, and of those covered by the monographs particularly. Such monographs will appear on drugs representing new chemical entities for which suitable identity tests and assay procedures are not available in the published literature. The purity and assay limits reported for the drugs and their dosage forms are based on observations made on samples representative of commercial production and are considered to be reasonable within expected analytical and manufacturing variation.

CALCIUM 3-(dimethylaminomethyleneamino)-2,4,6-triiodohydrocinnamate; $C_{24}H_{24}CaI_6N_4O_4$; mol. wt. 1233.99. Calcium ipodate may occur also as the dihydrate. The structural formula of calcium ipodate (anhydrous) may be represented as



Physical Properties.—Calcium ipodate occurs as a white to off-white, odorless, fine crystalline powder. It is slightly soluble in alcohol, in chloroform, in methanol, and in water.

Identity Tests.—Heat about 500 mg. of calcium ipodate in a porcelain crucible over a free flame: violet vapors of iodine are evolved.

Dissolve about 200 mg. of calcium ipodate in 10 ml. of 30% acetic acid, and add 2 ml. of ammonium oxalate T.S.: a white precipitate of calcium oxalate, which is soluble in diluted hydrochloric acid, results.

A 1 in 100,000 solution of calcium ipodate in methanol exhibits an ultraviolet absorbance maximum at about 235 mμ [absorptivity (1%, 1 cm.) about 600]. The spectrum is shown in Fig. 1.

The infrared spectrum of a 0.5% dispersion of calcium ipodate in potassium bromide, in a disk of about 0.82 mm. thickness, is shown in Fig. 2.

Purity Tests.—Determine the water content of calcium ipodate by the titrimetric (Karl Fischer) method: not more than 3.5% is found.

Dissolve about 200 mg. of calcium ipodate in 10 ml. of 30% acetic acid, add 1 ml. of chloroform, and shake vigorously. Allow the layers to separate: the chloroform layer shows no violet color (absence of free iodine). Add 1 ml. of 0.1 *N* potassium iodate solution and shake vigorously. Allow the layers to separate: the chloroform layer shows no trace of violet color (absence of iodide ion).

Determine the heavy metals content of calcium

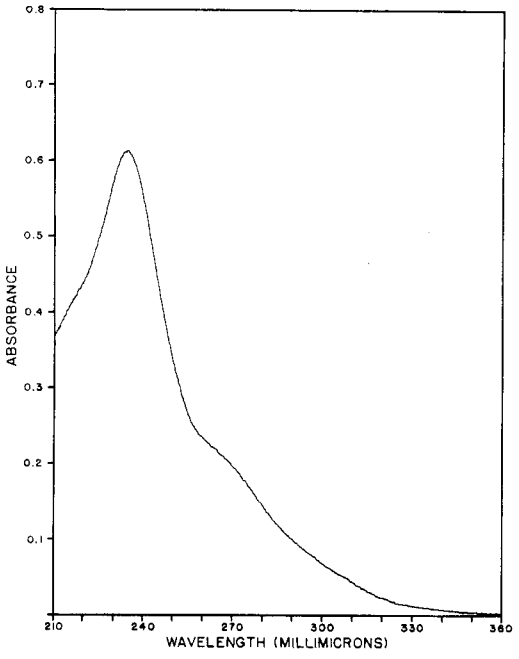


Fig. 1.—Ultraviolet absorption spectrum of calcium ipodate in methanol (10 mcg./ml.); Beckman model DK-2A spectrophotometer.

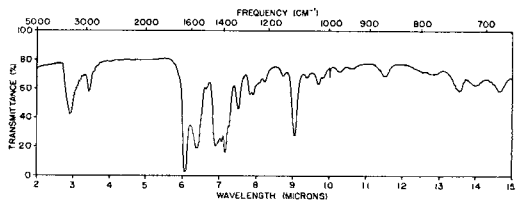


Fig. 2.—Infrared spectrum of calcium ipodate in potassium bromide disk (0.5%); Perkin-Elmer model 21 spectrophotometer, sodium chloride prism.

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ipodate by the U.S.P. XVI heavy metals test, method II. The heavy metals limit for calcium ipodate is 30 p.p.m.

Assay.—Transfer about 300 mg. of calcium ipodate, accurately weighed, to a glass-stoppered, 250-ml. flask, add 30 ml. of sodium hydroxide solution (1 in 20) and 500 mg. of powdered zinc, connect the flask to a reflux condenser and reflux the mixture for 30 min. Cool to room temperature, wash the condenser with 20 ml. of water, and filter the mixture. Wash the flask and the filter with small portions of water, adding the washings to the filtrate. Add to the filtrate 5 ml. of glacial acetic acid and 3 drops of eosin Y T.S., and titrate with 0.05 *N* silver nitrate until the entire mixture changes to a permanent pink color. Each milliliter of 0.05 *N* silver nitrate is equivalent to 6.345 mg. of iodine (I), and to 10.28 mg. of $C_{24}H_{24}CaI_6N_4O_4$. The amount of calcium ipodate found, calculated on the anhydrous basis, is not less than 97.5% and not more than 102.5% of the weight of the sample taken.

DOSAGE FORMS OF CALCIUM IPODATE

Calcium Ipodate Granules

Identity Tests.—Transfer to a beaker an amount of calcium ipodate granules equivalent to about 2 Gm. of calcium ipodate, add 100 ml. of water and stir for several minutes. Filter the suspension with the aid of suction and wash the filter with several small portions of water. Dry the residue of calcium ipodate in a vacuum oven at 60° for 4 hr. The residue responds to the identity tests in the monograph for calcium ipodate.

Assay.—Accurately weigh the contents of not less than 10 packets of calcium ipodate granules, and mix well. Transfer an accurately weighed portion of the granules, equivalent to about 300 mg. of calcium ipodate, to a glass-stoppered, 250-ml. conical flask and proceed as directed in the assay under calcium ipodate beginning with "... add 30 ml. of sodium hydroxide solution (1 in 20) ..." Each milliliter of 0.05 *N* silver nitrate is equivalent to 10.28 mg. of $C_{24}H_{24}CaI_6N_4O_4$. The amount of calcium ipodate found is not less than 85.0% and not more than 115.0% of the labeled amount.

DISCUSSION

Calcium ipodate[1] is an oral radiographic contrast medium for cholangiography and cholecystography.

A brief discussion of the identity tests and quantitative methods may be found in the monograph for sodium ipodate (1).

The assay of bulk calcium ipodate gave an average value of 99.7 ± 0.1%,[2] equivalent to 61.5 ± 0.1%[2] iodine (I). Analysis of commercial 3-Gm. packets gave an average value of 87.9 ± 1.9%[2] of the labeled amount of calcium ipodate.

REFERENCE

(1) *J. Pharm. Sci.*, **54**, 909(1965).

[1] Marketed as Oragrafin Calcium by E. R. Squibb and Sons New York, N. Y.

[2] Maximum deviation from the mean value.

Chromatographic Analysis of Phenobarbital and Belladonna Alkaloid Combinations

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A partition column chromatographic technique is applied to the analysis of phenobarbital and the belladonna alkaloids as found in commercial tablets and elixirs. Separation is achieved on a Celite column in which the stationary phase is a 10 per cent solution of *p*-toluenesulfonic acid. Ether and chloroform elute phenobarbital and the alkaloid–*p*-toluenesulfonic acid complex, respectively. The isolated phenobarbital is determined spectrophotometrically, and the total belladonna alkaloids are measured colorimetrically by a modification of a published procedure. A study of the modifications is reported and statistically evaluated. Standard recoveries averaged 99.01 per cent for phenobarbital and 98.73 per cent for atropine sulfate.

THE BELLADONNA alkaloids are commonly formulated in combination with phenobarbital.[1] Current analytical procedures for the assay of such a specific formulation appear to be limited to conventional extraction-titration methods (1), although many techniques have been reported for the assay of a variety of mixtures containing only one of the components.

Methods for the determination of atropine in combinations include several titration or colorimetric determinations (2), some of which are utilized in the official compendia. Basu and Dutta (3) separated morphine from atropine with reineckate salts at controlled pH values. Ion-exchange resins have been successfully utilized by several investigators in the isolation

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[1] This paper is concerned with those preparations compounded with the salts of the individual alkaloids, atropine, hyoscyamine, and hyoscine. Products containing fluidextract or tincture of belladonna were not included in these studies.