Rapid and Simplified Assay for Thyroid in Pharmaceutical Preparations by Potentiometric Titration

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Abstract □ A procedure for the determination of thyroid (thyroid hormone) in pharmaceutical preparations by titration with 1 m*M* silver nitrate using an ion-selective electrode was developed and evaluated. Samples were combusted according to the USP procedure and analyzed with a minimum of work-up for iodine content. The results obtained by this method were compared with those obtained by the official methods. The recovery of iodide from spiked placebo samples was investigated. The method is applicable to content uniformity analyses as well as to bulk material and to the analysis of organically bound iodide in other pharmaceutical preparations such as sodium levothyroxine tablets. The method is fast, simple, accurate, applicable to automation, and is suitable for routine quality control use.

Keyphrases □ Thyroid—determination in pharmaceutical preparations, potentiometric titration of iodide □ Thyroid and sodium levothyroxine analyses—assay by potentiometric titration, content uniformity analyses

The USP XX method (1) for the assay of thyroid (thyroid hormone) in tablets and bulk material involves combustion of the samples at 675–700° with potassium carbonate followed by oxidation under acidic conditions to iodate by heating with excess bromine. The addition of potassium iodide converts the iodate to iodine, which is then titrated with sodium thiosulfate (2). The method for content uniformity analyses involves oxygen flask combustion followed by conversion of the iodine to triiodide ion and spectrophotometric determination. These methods are lengthy and filled with difficulties.

This report describes a simplified method for the assay of organically bound iodide, which uses an iodide-selective electrode (3–6). The method is applicable to the analysis of not only thyroid in tablets and bulk material but also to other pharmaceutical preparations in which organically bound iodine is determined.

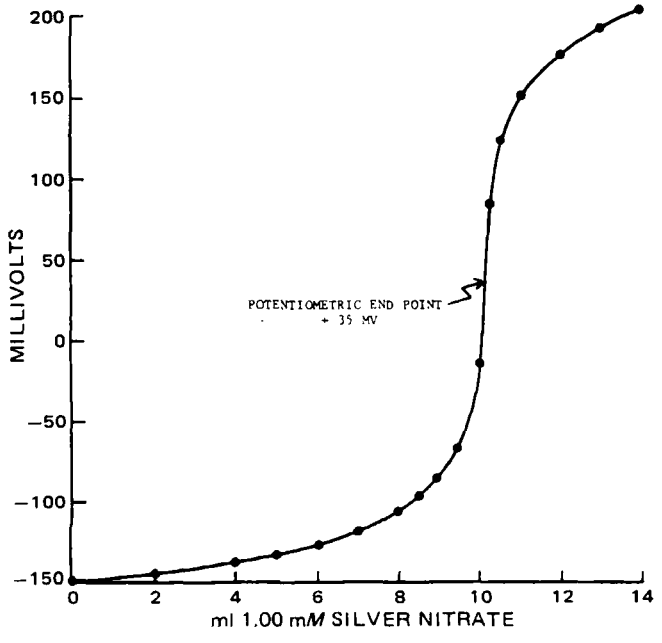

Figure 1—*Titration curve of a titrated thyroid sample containing ~0.01 meq of iodide with 1.00 m*M *silver nitrate using an iodide-sensing electrode, pH 2.5. Arrow indicates potentiometric end point + 35 mV.*

EXPERIMENTAL

Reagents and Materials—Sodium iodide reference standard (0.100 *M*)[1] was used as received or diluted as required with water; 1.00 m*M* silver nitrate solution was prepared by dilution of 0.100 *M* silver nitrate solution[2] and standardized by potentiometric titration against 1.00 m*M* iodide standard. This solution is quite stable if protected from light. Anhydrous potassium carbonate[3] was technical grade; dilute phosphoric acid was made by 1:1 dilution of reagent grade (85%) phosphoric acid[4]; deionized water[5] was used throughout; crucibles were porcelain[6] and all other tablet excipients were pharmaceutical grade and obtained commercially. The thyroid tablets were manufactured by Pharmaceutical Basics, Inc.

Apparatus and Equipment—A muffle furnace[7] was used for sample combustion. The specific ion electrodes used were an iodide-sensing electrode[8] and a silver-sulfide-sensing electrode[9]; the reference electrode was a double-junction type[10]. The potentiometric titrations were performed either automatically or manually to a predetermined millivolt end point using an end-point titrator fitted with a 20-ml dispensing buret unit and an antidiffusion buret tip[11].

Sample Preparation—*Uncoated Tablets and Bulk Material*—Twenty tablets were ground to a fine powder and a portion equivalent to ~635 mg of thyroid (proportionately less should be used if the iodine content is >0.2%) was weighed into a large crucible; this portion was mixed with ~8 g of anhydrous potassium carbonate, compressed, and then overlayed with 16 g of carbonate. The mixture was ignited at 675–700° in a preheated muffle furnace for 25 min. The cooled char was transferred to a 600-ml beaker, using water to facilitate the transfer, and then acidified to pH 2.5 ± 1 with dilute phosphoric acid while stirring vigorously with a magnetic stirrer. Water was added to bring the volume to 400 ml, and the mixture was titrated immediately with 1 m*M* silver nitrate to the potentiometric end point using an iodide-sensing electrode and a suitable reference electrode. (Each milliliter of 1 m*M* silver nitrate is equivalent to 0.1269 mg of iodine.)

Coated Tablets—The coated sample was prepared in the same way as the uncoated tablets except that the char was treated with hot water, filtered and then acifidied with dilute phosphoric acid, and the volume brought to 400 ml with water. (If calcium sulfate is used in the formulation, the acidified solution is boiled for at least 30 min.) The solution was cooled to room temperature and titrated with 1 m*M* silver nitrate to the potentiometric end point.

Content Uniformity Analyses—The procedure for uncoated or coated tablets was followed, except that 10 tablets were individually analyzed.

Sodium Levothyroxine Tablets—Twenty tablets were finely powered and an amount equivalent to 1–2 mg of sodium levothyroxine was weighed into a crucible. The procedure for uncoated tablets was followed

[1] Orion Research, Cambridge, Mass.
[2] Dilut-It, J. T. Baker Chemical Co., Phillipsburg, N.J.
[3] Diamond Shamrock Corp., Irving, Tex.
[4] J. T. Baker Chemical Co., Phillipsburg, N.J.
[5] Continental Water Conditioning Corp., Denver, Colo.
[6] Coors Porcelain, Golden, Colo.
[7] Thermolyne 2000, Sybron Corp., Dubuque, Iowa.
[8] Orion Research, Model 94-53.
[9] Orion Research Model 94-16.
[10] Orion Research Model 90-20.
[11] Metrohm/Brinkmann model E526 Titrator and model 655 Dosimat, Westbury, N.Y.

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Table I—Percentage of Iodine in a 130-mg Thyroid Tablet by the USP XX Method and by the Proposed Method in the Presence and Absence of Charcoal

	USP XX Method	Proposed Method No Charcoal	Proposed Method With Charcoal
Iodine, %	0.190	0.190	0.190
Number of determinations	12	16	11
Range, %	0.175–0.199	0.180–0.202	0.180–0.201
RSD, %	4.6	3.6	3.4

except that each milliliter of 1 m*M* silver nitrate was equivalent to 0.1997 mg of sodium levothyroxine.

RESULTS AND DISCUSSION

Figure 1 shows the titration curve obtained with a typical thyroid sample containing ~0.01 meq of iodide is titrated with 1 m*M* silver nitrate using an iodide-sensing electrode and a suitable reference electrode. The end point occurs at about +35 milivolts mV in this sample but may vary according to the electrode pair used. A similar curve is obtained using a silver-sensing electrode. The iodide electrode can also be used to quantitatively measure inorganic iodide in thyroid preparations. Changing the pH of the solution from 1.5 to 3.5 has very little effect on the overall titration curve and the end point (± 5 mV). For content uniformity determinations of low-strength thyroid preparations (16–65 mg), the curve is shifted somewhat to a lower millivolt end point. Therefore, it is advisable to determine the end point of such samples in advance by titrating a representative sample and plotting the titration curve. Since the break in the curve near the end point is sharp, and since there is a change of almost 200 mV within ±0.5 ml of the end point, it is practical to titrate thyroid samples automatically using either an end-point titrator or recording titrator. It is also possible to perform the titrations manually using a pH–mV meter and buret to the predetermined end point.

Comparison of the USP XX Method—A 130-mg (2 gr) uncoated thyroid tablet was assayed by potentiometric titration and by the USP XX method. The results are shown in Table I and indicate that this method gives results equivalent to the USP method. Filtration of the charcoal produced in the combustion process is not necessary for ordinary compressed tablets if the sample is titrated immediately. However, stirring the sample in the presence of charcoal at pH 2.5 slowly oxidizes the iodide. In addition to this tablet, numerous lots of thyroid tablets (both coated and uncoated) and capsules and bulk material were assayed by both the USP and potentiometric titration methods. The two methods agreed closely, although the proposed method gave somewhat more consistent results, which were also closer to the theoretical input.

Recovery of Iodide from Spiked Placebos—Placebo mixtures containing excipients found in typical coated and uncoated thyroid tablets were prepared and spiked with iodide over the range of 0.0085–0.0115 meq (equivalent to 0.17–0.23% iodine). The recovery of iodide from the spiked samples was quantitative, and the relative standard deviations (*RSD*) of the recoveries varied from 0.58 to 1.24%. Linearity was excellent (r = 1.00), and placebo blanks showed that there was no interference from the tablet excipients (millivolt reading past the end point). The results are summarized in Table II.

Table II—Recovery of Iodide Added to Placebo Preparations

	Coated Tablet with Calcium Sulfate	Coated Tablet with Calcium Carbonate	Uncoated Tablet
Mean recovery, %	99.5	99.8	100.0
Number of determinations	10	13	16
Range, %	97.3–101.2	97.7–101.3	98.7–100.6
RSD, %	1.24	1.40	0.58

Table III—Recovery of Iodide Added to Content Uniformity Placebo Preparations

	16-mg Uncoated Tablet, 0.00025 meq Iodide Spike	65-mg Coated Tablet, 0.001 meq Iodide Spike	195-mg Uncoated Tablet, 0.003 meq Iodide Spike
Average recovery, %	98.9	100.9	100.7
Number of determinations	10	10	10
Range, %	96.0–104.0	98.8–103.7	98.4–101.9
RSD, %	3.33	1.60	1.60

Effect of Calcium Sulfate—When calcium sulfate is used in the formulation of coated tablets, sulfide is produced in the combustion process. Since sulfide interferes with both the iodide and silver-sensing electrodes, methods were investigated to remove this interfering ion. The addition of heavy metals, such as Ni(II), was not successful in removing the interference, while addition of hydrogen peroxide oxidized the sulfide but also slowly oxidized the iodide. Boiling of the filtered, acidified solution was found to be an acceptable method for removing the interfering sulfide. However, in samples with less sulfide, such as content uniformity samples, the boiling step can be eliminated by acidifying the char before filtration. Apparently the charcoal produced in the combustion process oxidizes the sulfide to a noninterfering form (possibly persulfide), since the addition of ascorbic acid again generates sulfide.

Content Uniformity Assays—The described method has been successfully applied to routine quality control work for content uniformity determinations of tablets ranging in potency from 16 to 324 mg of thyroid. For low-potency tablets the volume of titrant is small and the electrode response is slower; such samples may require manual titration. Table III summarizes the results obtained when placebo samples spiked with 0.00025, 0.001, and 0.003 meq of iodide (corresponding to 16-, 65-, and 195-mg tablets) are assayed by the present method. The results indicate that recovery of the added iodide is quantitative and that reproducibility is good.

Analysis of Sodium Levothyroxine Tablets—The above procedure provides a fast and accurate method for the analysis of sodium levothyroxine (I) in tablets. Sample preparation is the same as for uncoated thyroid tablets, except that an amount of powered tablets equivalent to 1–2 mg of I is used. Mean recoveries of I added to placebo mixtures were 99.8% (11 determinations; *RSD* 1.8%) for a 0.1-mg preparation and 99.2% (six determinations; *RSD* 0.7%) for a 0.3 mg tablet. Linearity of the method in both cases was excellent (r = 0.99).

REFERENCES

(1) "The United States Pharmacopeia," 20th rev., U.S. Pharmacopieal Convention, Rockville, Md., 1980, pp. 800–801.

(2) A. H. Beckett and J. B. Stenlake, "Practical Pharmaceutical Chemistry," Athlone, London, 1962, pp. 141–142.

(3) W. L. Hoover, J. R. Melton, and P. A. Howard, *J. Assoc. Off. Agric. Chem.*, **54**, 760 (1971).

(4) B. Paletta and K. Panzebeck, *Clin. Chim. Acta*, **26**, 11 (1969).

(5) B. Paletta, *Mikrochim. Acta*, **6**, 1210 (1969).

(6) U. Westerlune-Helmerson, *Anal. Chem.*, **43**, 1120 (1971).