Estimation of Diiodohydroxyquin in Nonaqueous Media

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Abstract □ A method for estimating diiodohydroxyquin in dosage forms by nonaqueous titration was developed. Acetic anhydride was the most suitable solvent for titration.

Keyphrases □ Diiodohydroxyquin formulations—nonaqueous titrimetric analysis □ Titrimetry, nonaqueous—analysis, diiodohydroxyquin

The development of new drugs has encouraged the introduction of new methods of analysis and control. The importance of assay methods involving nonaqueous titration cannot be overemphasized. Since the estimation of active ingredients in medicinal dosage forms may not be carried out as smoothly as with active ingredients in the absence of excipients and other inactive additives, some modifications in the method of estimation may be necessary.

Diiodohydroxyquin (I) is a well-known amebicide. It has been recommended in the treatment of lambliasis, balantidal dysentery, and trichomonas vaginitis. Reports have appeared on the estimation of diiodohydroxyquin by colorimetry (1), polarography (2), the oxygen flask method (3), and iodometry (4). Feltkamp (5) determined iodochlorhydroxyquin (5-chloro-7-iodo-8-hydroxyquinoline) by nonaqueous titration. Some of the mentioned methods have been made official, but no work seems to have been reported for the estimation of I by nonaqueous titration.

Table I—Analysis of I in Dosage Forms (Synthetic Mixture)

Synthetic Tablet Mixture	Mixture Constituents	Amount[a], mg.	Recovery[b], %
1	I	300	100.4 ± 0.3
	Starch	30	
	Talc	2	
	Lactose	60	
2	I	300	101.1 ± 0.32
	Sugar	20	
	Sodium alginate	10	
	Starch	10	
	Stearic acid	2	
	Lactose	50	

[a] About 300 mg. accurately weighed I was taken each time. [b] Each figure represents the mean of five readings.

Table II—Analysis of I in Tablets (Manufactured Preparations)

Manufacturer	Drug	Labeled Amount	Recovery[a], %
—	I	—	100.1 ± 0.6
A	I	300 mg./tablet	100.15 ± 0.32
B	I	300 mg./tablet	100.32 ± 0.18

[a] Each figure represents the mean and standard deviation of at least five readings.

In the present study, an attempt was made to find a suitable method of estimation of I as such and in dosage forms in nonaqueous media.

EXPERIMENTAL

A pH meter[1] using a glass electrode[2] and a saturated calomel electrode was used. The aqueous potassium chloride solution in the saturated calomel electrode was replaced by a saturated solution of lithium chloride in acetic acid. The electrode pair was dipped in acetic anhydride for at least 24 hr. before use. The solvents and reagents used were of analytical reagent grade. Malachite green (0.3%) solution in acetic acid was used as the indicator.

Estimation of I in Dosage Forms—About 300 mg. of accurately weighed I was placed in a conical flask and dissolved in 30 ml. of acetic anhydride by heating. The solution was cooled to room temperature, 3–5 drops of Malachite green indicator was added, and the mixture was titrated by 0.1 *N* perchloric acid in acetic acid to a yellow end-point. A blank was performed, and an appropriate correction was made. Each milliliter of 0.1 *N* perchloric acid is equivalent to 0.039698 g. of diiodohydroxyquin. (The end-point was checked potentiometrically using glass and modified calomel electrode pairs.)

Synthetic Mixture—About 300 mg. of accurately weighed I was placed in a conical flask. The various excipients were added in the amounts occurring generally in tablet formulations. Acetic anhydride (30 ml.) was added, and the solution was heated to dissolve the drug (excipients settled). The titration was performed as described for the estimation of I in pure form, commencing with the words: "3–5 drops of Malachite green . . . ."

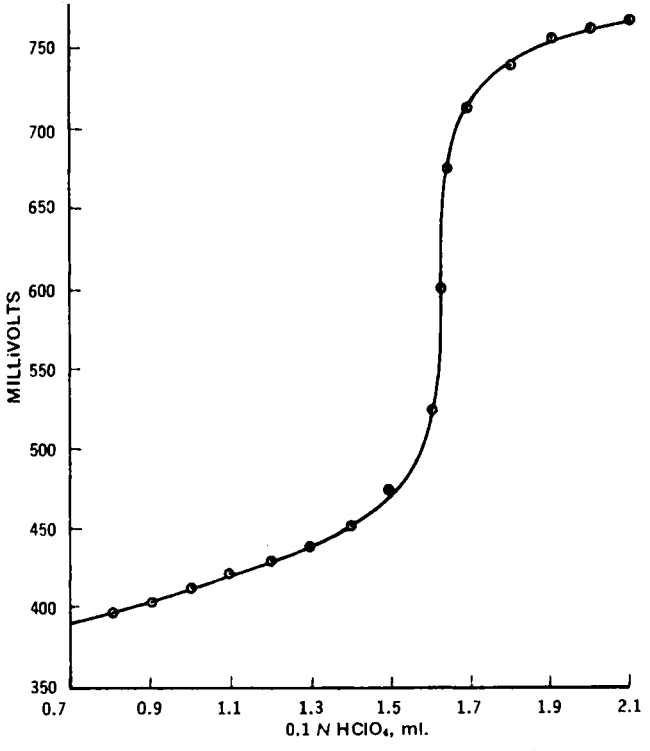

Figure 1—*Titration curve of diiodohydroxyquin (67.5 mg.).*

[1] Systronics Type 322.
[2] Toshniwal.

Table III—Analysis of I in Dosage Forms (Manufactured Preparations)

Drug	Labeled Amount	Recovery[a], % Proposed Method, Non-aqueous Titration	Official Method	Colorimetry
I	—	100.1	97.3	99.1
I	300 mg./tablet	100.3	98.2	99.3

[a] Each figure represents the mean of at least five readings.

Manufactured Preparations—Twenty tablets were weighed and reduced to a fine powder. An accurately weighed quantity of powder, equivalent to 300 mg. of I was added to 30 ml. of acetic anhydride. The mixture was then gently heated (excipients settled). After cooling to room temperature, the titration was performed as described for the estimation of I in pure form, commencing with the words: "3–5 drops of Malachite green. . . ."

RESULTS AND DISCUSSION

The nature of the titration curve of I is shown in Fig. 1. In the preliminary trials, the estimation of this drug in acetic acid resulted in overestimation, probably due to the consumption of perchloric acid by certain excipients. However, on using acetic anhydride as the solvent with Malachite green as the indicator, the end-point was sharp and the recoveries were better than with acetic acid. The color change of the indicator was checked potentiometrically. Tables I and II show the recovery.

Table III shows the results obtained by the proposed method, by the official method (4), and by colorimetry (1). It is apparent from these data that good recoveries were achieved by nonaqueous titration. The official method is a time-consuming and cumbersome procedure with lower recoveries. In the colorimetric method, Beer's law is obeyed in a very narrow range (0.05–0.3 mg.) and the recovery of the drug is not satisfactory. The proposed nonaqueous method of titration is a rapid and simple technique, giving accurate results.

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Assay of Thiotepa by PMR Spectrometry

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Abstract □ A rapid (10 min.), accurate, and precise (SD = 0.6%) analytical method for thiotepa and thiotepa for injection involving PMR is described. The procedure, which was tested on two spectrometer models, employs an inexpensive solvent and internal standard and does not require preparative treatment.

Keyphrases □ Thiotepa—PMR analysis, aziridinyl protons □ Aziridinyl derivatives—PMR analysis of thiotepa □ PMR spectroscopy—analysis, thiotepa

During the characterization of potential oncolytics, the methylene protons of aziridinyl moieties present in some of these agents were readily detected by proton magnetic resonance (PMR) spectrometry. This observation led to an interest in the quantitative analysis of an official drug by this instrumental method. Thiotepa [*N,N',N''*-triethylenethiophosphoramide, tris(1-aziridinyl)phosphine sulfide] meets the criteria of a good candidate for assay by PMR spectrometry because it is soluble in an inexpensive, nondeuterated solvent and gives a simple spectrum. In addition, the assay procedure presented here, in contrast to other PMR drug analysis (1, 2), does not require processing of the sample prior to instrumental examination; in view of this drug's chemical lability, this is especially advantageous. Only additions of an internal standard and solvent to the sample are required. Although thiotepa is a low dosage pharmaceutical, giving solutions of about 1.9% concentration in this assay, the integral values for the peak areas can be measured with sufficient accuracy and precision.

All of these factors provide for a simple, accurate, and rapid analytical method for thiotepa and this pharmaceutical's parenteral formulation. The USP XVIII procedures for these items involve lengthy and laborious titrimetric and IR spectrophotometric methods, respectively. To determine the capabilities of different

Table I—Analysis of Thiotepa Standards by PMR

Sample	Internal Standard, mg.	Thiotepa, Added, mg.	Thiotepa, Found, mg.	Thiotepa, Recovered, %
1	23.63	15.16	15.41	101.6
2	23.45	15.95	16.13	101.1
3	24.26	14.76	14.71	99.7
4	23.88	14.83	15.12	102.0
5	23.15	17.80	18.01	101.2
6	23.78	15.37	15.41	100.3
7	23.38	15.07	15.37	102.0
8	23.66	15.20	15.38	101.2
Mean and standard deviation			101.1 ± 0.6	