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Nonaqueous Titrimetric Determination of Isoniazid in Presence of Excess of Sodium *p*-Aminosalicylate in Dosage Forms

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Abstract □ Isoniazid in the presence of excess of sodium *p*-aminosalicylate is estimated by differential titration of the acetonitrile extract of the mixture against perchloric acid. Sodium *p*-aminosalicylate content is then calculated from the total basicity obtained by direct titration of the mixture with the same titrant. The procedure is applied to determine the isoniazid and sodium *p*-aminosalicylate content of tablets, granules, and cachets. The results obtained are comparable to those obtained by the official method.

Keyphrases □ Isoniazid, Na *p*-aminosalicylate mixture—analysis □ Differential titration, nonaqueous—analysis □ Perchloric acid—titrant

Commercial dosage forms of isoniazid–sodium *p*-aminosalicylate combinations usually contain the components in molar proportions of 1:33. The conventional methods for the analysis of these dosage forms give erroneous and inconsistent results (1, 2).

Differential titration of isoniazid–sodium *p*-aminosalicylate mixture has been described earlier (3). The method is restricted only to the analysis of the mixtures having sodium *p*-aminosalicylate-to-isoniazid ratio up to 4:1.

In the present study, mixtures having large disproportion of the components were extracted with acetonitrile to remove the bulk of sodium *p*-aminosalicylate. The molar proportion of sodium *p*-aminosalicylate-to-isoniazid in the acetonitrile extract was favorable for the differential nonaqueous titration of these compounds. The nonaqueous titrimetric procedure described earlier (3) was applied to estimate isoniazid in the presence of sodium *p*-aminosalicylate in the acetonitrile extract and found to give satisfactory recovery of isoniazid. Sodium *p*-aminosalicylate content of the mixture was determined from total basicity obtained by direct titration of the mixture.

The procedure was applied to the analysis of tablets, granules, and cachets and the results were found comparable to those obtained by the official method (4).

Table I—Recovery of Isoniazid in the Presence of Excess Sodium *p*-Aminosalicylate

Amt. Weighed, meq.		Recovery, %	
Isoniazid	Sodium *p*-Aminosalicylate	Isoniazid[a]	Sodium *p*-Aminosalicylate[b]
0.1	0.5	100.42 ± 0.42[c]	99.90 ± 0.50
0.1	1.0	100.10 ± 0.39	100.00 ± 0.41
0.1	2.0	99.75 ± 0.52	100.10 ± 0.39
0.1	3.0	99.85 ± 0.47	99.73 ± 0.52
0.1	4.0	99.50 ± 0.37	99.85 ± 0.40
0.1	5.0	100.52 ± 0.53	99.95 ± 0.61

[a] Isoniazid content was determined from the titration of acetonitrile extract of the mixture. [b] Amount of sodium *p*-aminosalicylate was estimated from the total basicity of the mixture determined by direct titration, as described, after subtraction of the volume of titrant corresponding to isoniazid content of the mixture. [c] Standard deviation based on at least five determinations.

EXPERIMENTAL

Apparatus and Reagents—The reagents and apparatus were employed as described previously (3). The electrodes were dipped in acetic anhydride for 24 hr. before use.

Analysis of Mixtures Containing Isoniazid and Excess of Sodium p-Aminosalicylate—*Isoniazid*—Milliequivalent quantities of finely powdered isoniazid and sodium *p*-aminosalicylate as given in Table I were accurately weighed and transferred to a 100-ml. beaker. After adding 25 ml. of acetonitrile, the mixture was stirred vigorously for 20 min. and filtered. The residue in the beaker was treated with 10 ml. acetonitrile and stirred for 5 min. and filtered. It was further washed twice with 5 ml. of acetonitrile. An equal volume of acetic anhydride was added to the combined filtrates and washings. The mixture was stirred for 5 min. It was then titrated against 0.1 *N* acetous perchloric acid. Near the second end point, 0.05 ml. of titrant was added at an interval of 1 min. A blank titration was performed. Titration curves were obtained by plotting potential reading (mv.) *versus* volume (ml.) of the titrant.

Total Basicity—An aliquot of the mixture equivalent to 0.25 meq. of sodium *p*-aminosalicylate was accurately weighed and transferred to a 100-ml. beaker. Acetonitrile (25 ml.) was added to it and stirred. After addition of an equal volume of acetic anhydride, it was titrated as described previously.

Analysis of Dosage Forms—The procedure was applied to analyze the powder mass obtained from tablets, granules and cachets.

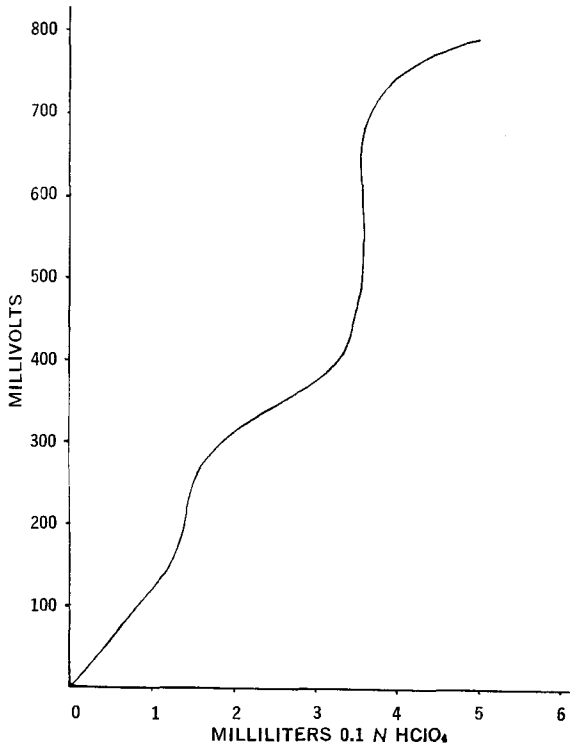

Figure 1—*Typical titration curve of acetonitrile extract of isoniazid–sodium* p*-aminosalicylate (1:50) mixture after diluting it with equal volume of acetic anhydride.*

Where magnesium stearate was used as a lubricant in the preparation of tablets, the aliquot of tablet mass equivalent to 0.25 meq. of sodium *p*-aminosalicylate was mixed with salicylaldehyde (3.0 ml.) and treated three times with 10-ml. quantities of acetonitrile and filtered. The combined filtrates were then diluted with equal volume of acetic anhydride and titrated as described to obtain reading for total basicity.

RESULTS AND DISCUSSION

At the very outset, it was evident that because of the large excess of sodium *p*-aminosalicylate associated with isoniazid in commercial dosage forms, a direct differential nonaqueous titrimetry would be of no avail (3).

The quantitative extraction of isoniazid–sodium *p*-aminosalicylate mixture has been attempted by several workers (5–7). However, either the separation of the components was not efficient or the procedure adopted was time consuming.

In the present work, advantage was taken of the difference in solubilities of these compounds in acetonitrile to obtain molar ratio of the components in the extract favorable for differential titration. Thus, the removal of the bulk of sodium *p*-aminosalicylate was effected by extracting the mixture with acetonitrile. The acetonitrile extract contained only a part of sodium *p*-aminosalicylate but the whole of isoniazid. The end points for both the components could be resolved in the titration of acetonitrile extract (after diluting it with equal volume of acetic anhydride) against acetous perchloric acid.

A typical titration curve thus obtained is reproduced in Fig. 1. The first inflection in the curve (see Fig. 1) corresponds to the sodium *p*-aminosalicylate while the second inflection denotes the end point corresponding to isoniazid present in the extract.

Acetonitrile extracts of a number of mixtures were analyzed by the proposed procedure for their isoniazid content (see Table I).

Table II—Analysis of Dosage Forms Containing Isoniazid and Sodium *p*-Aminosalicylate by Various Procedures

Dosage Form		Active Ingredients Labeled	Amt.,[a] mg.	Recovery in mg. By—Known Method Isoniazid	Known Method Na-PAS	Proposed Method Isoniazid	Proposed Method Na-PAS
Tablet	A	Isoniazid	25.0	24.3	840.0	24.0	845.0
		Na-PAS	834.0				
Tablet	B	Isoniazid	25.0	20.0	835.0	20.2	839.0
		Na-PAS	850.0				
Tablet	C	Isoniazid	30.0	29.0	995.0	29.3	1000.0
		Na-PAS	1000.0				
Tablet	D	Isoniazid	26.7	26.6	851.0	26.2	846.0
		Na-PAS	850.0				
Granules	A	Isoniazid	25.0[b]	25.2	782.0	25.5	788.0
		Na-PAS	780.0[b]				
Granules	B	Isoniazid	23.3[b]	23.5	779.1	23.1	776.0
		Na-PAS	777.0[b]				
Cachet	A	Isoniazid	33.0	33.0	1509.0	32.7	1500.0
		Na-PAS	1500.0				

[a] Per unit dosage. [b] Per gram of the granules.

The recovery of isoniazid from synthetic mixtures having sodium *p*-aminosalicylate-to-isoniazid ratio as high as 50:1 was found to be satisfactory.

For the estimation of sodium *p*-aminosalicylate, an aliquot of the mixture dissolved in acetonitrile–acetic anhydride (1:1) mixture is titrated against acetous perchloric acid. Only one inflection point in the titration curve is obtained which corresponds to total basicity of the mixture. The amount of sodium *p*-aminosalicylate present in the mixture can be calculated from the reading for the total basicity of the mixture after subtracting the volume of the titrant required for isoniazid.

The procedure was applied to analyze commercial dosage forms. The results agreed closely with those obtained by the official method (4) (see Table II). The usual diluents, lubricants, and colors used in the preparation of dosage forms did not appear to interfere with the titration. However, the presence of magnesium stearate in tablets as lubricant induces high recoveries of sodium *p*-aminosalicylate. In such a case, the sample of the powdered tablet was treated with salicylaldehyde and extracted with acetonitrile. The solubility of sodium *p*-aminosalicylate increases in the presence of salicylaldehyde, so that its complete extraction is effected with a relatively small volume of solvent. The extract after diluting with equal volume of acetic anhydride is titrated as usual. The method gave satisfactory recovery of sodium *p*-aminosalicylate.

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