

Differential Nonaqueous Titration of Isoniazid and Sodium *p*-Aminosalicylate Mixtures

M. B. DEVANI and C. J. SHISHOO

Abstract □ Isoniazid and sodium *p*-aminosalicylate are estimated potentiometrically in nonaqueous media. Their mixtures are amenable to differential nonaqueous titrimetry. The titration solvent consists of a mixture of equal volumes of acetonitrile and acetic anhydride, the titrant is acetous perchloric acid, and electrode system is the glass-calomel electrode pair. Satisfactory resolution of end points is obtained with the ratio of sodium *p*-aminosalicylate-to-isoniazid as high as 4:1. Both of these components in mixtures can be determined in a single titration by the proposed method without resorting to preliminary separation.

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

A variety of chromatographic, volumetric, colorimetric, spectrophotometric, and nonaqueous titrimetric procedures have been described for the analysis of isoniazid as well as sodium *p*-aminosalicylate (1–3).

The individual components in mixtures are generally determined after initial separation by one of these

methods (4–6). Although satisfactory results can be obtained by these methods, they suffer from several drawbacks, particularly that of time-consuming preliminary separation processes. While isoniazid and sodium *p*-aminosalicylate can be readily determined in nonaqueous media individually, their differential titration in a mixture has not been reported.

The present study has been directed to find a simple differential nonaqueous titration procedure for the analysis of isoniazid–sodium *p*-aminosalicylate combinations. The mixtures having sodium *p*-aminosalicylate-to-isoniazid ratio up to 4:1 are resolved in a solvent system of acetonitrile–acetic anhydride (1:1). When the disproportionation ratio of the components is higher, only one end point corresponding to total base is realized.

PROCEDURE

Apparatus—All titrations were performed potentiometrically. A pH meter (Polymetron) employing a glass electrode and a calomel electrode with a salt bridge was used for the purpose. A saturated solution of lithium chloride in glacial acetic acid served as the salt bridge (7). Electrodes were dipped in acetic anhydride for at least 24 hr. before use.

Reagents and Solutions—Isoniazid BP was recrystallized from alcohol and dried at 105°. Sodium *p*-aminosalicylate USP was taken for analysis. Acetonitrile was purified by shaking it with two batches of silica gel (50 g./l.), two batches of alumina (20 g./l.), and phosphorus pentoxide (20 g./l.). Finally it was distilled over phosphorus pentoxide (5 g./l.) (8). Acetic anhydride reagent grade was distilled before use.

A 0.1 *N* solution of perchloric acid in glacial acetic acid was prepared and standardized potentiometrically against primary standard potassium acid phthalate dissolved in acetic acid. All other chemicals and solvents used in the study were reagent grade and were employed without further purification.

Analysis of Isoniazid—In a 100-ml. beaker about 60 mg. isoniazid, accurately weighed, was dissolved in 25 ml. of acetonitrile and stirred magnetically. An equal volume of acetic anhydride was added to it. The solution was further stirred for 5 min. and titrated potentiometrically against 0.1 *N* acetous perchloric acid. Near the

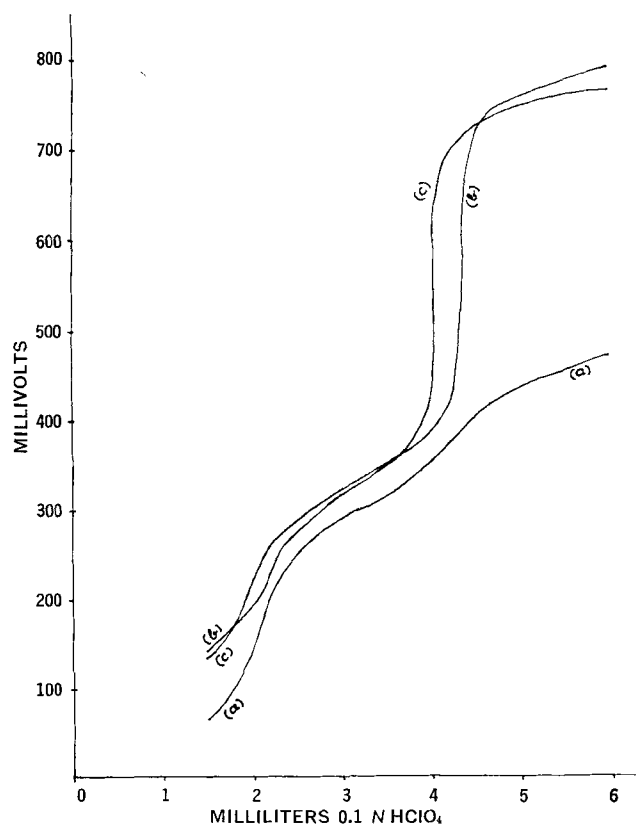


Figure 1—Titration curves of isoniazid–sodium *p*-aminosalicylate (1:1) mixture in various solvents against 0.1 *N* acetous perchloric acid. Key: a, acetonitrile; b, acetic anhydride; c, acetonitrile–acetic anhydride (1:1) mixture.

Table I—Effect of Isoniazid-to-Sodium *p*-Aminosalicylate Ratio on Sensitivity of Differentiating Titration

Amt. Weighed, meq.		Recovery, %	
Isoniazid	Sodium <i>p</i> -Aminosalicylate	Isoniazid	Sodium <i>p</i> -Aminosalicylate
0.3	—	99.9 ± 0.42 ^a	—
—	0.3	—	99.8 ± 0.37
0.2	0.1	99.9 ± 0.67	99.9 ± 0.48
0.2	0.15	98.9 ± 0.47	100.6 ± 0.56
0.1	0.1	99.6 ± 0.52	99.0 ± 0.87
0.1	0.2	99.7 ± 0.60	99.8 ± 0.72
0.1	0.3	100.0 ± 0.53	99.5 ± 0.64
0.1	0.4	100.0 ± 0.45	100.2 ± 0.76
0.1	0.5	One end point ^b	

^a Standard deviation based on at least five determinations. ^b Corresponds to isoniazid plus sodium *p*-aminosalicylate.

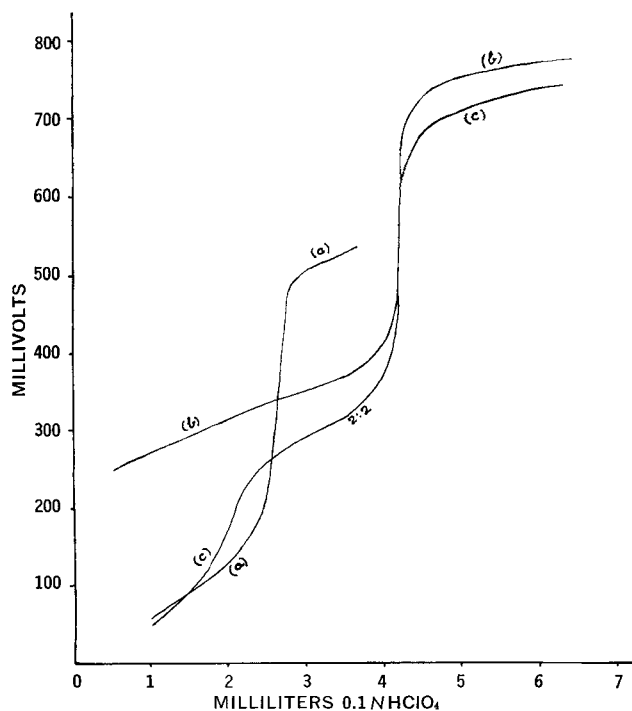


Figure 2—Titration curves using acetonitrile-acetic anhydride (1:1) mixture as solvent system. Key: a, sodium *p*-aminosalicylate 0.25 meq.; b, isoniazid 0.4 meq.; c, isoniazid-sodium *p*-aminosalicylate mixture containing 0.2 meq. of each component.

end point, titration was continued adding 0.05 ml. of titrant at intervals of 1 min. and the solution kept stirred vigorously. A blank titration was performed.

Titration curves were traced, plotting potential reading (mv.) versus volume of titrant (ml.).

Analysis of Sodium *p*-Aminosalicylate—About 60 mg. of sodium *p*-aminosalicylate, accurately weighed, was mixed with 25 ml. of acetonitrile in a 100-ml. beaker and stirred for about 15 min. An equal volume of acetic anhydride was then added and stirring continued further for 5 min. before the solution was titrated potentiometrically with 0.1 *N* acetous perchloric acid. The end point was determined from the titration curve as described earlier.

Differential Titration of Isoniazid-Sodium *p*-Aminosalicylate Mixture—About 0.1 meq. of isoniazid and 0.1 meq. of sodium *p*-aminosalicylate, accurately weighed, were mixed with 25 ml. acetonitrile and stirred for about 15 min. An equal volume of acetic anhydride (25 ml.) was added to it and the stirring was continued for about 5 min. The solution was titrated rapidly, stirring all the time, until the first end point was obtained. The titration was carried out slowly near the second end point. The exact end points were determined from the titration curve as before.

Effect of Isoniazid Concentration on Differential Titration—Isoniazid and sodium *p*-aminosalicylate, in varying proportions corresponding to desired ratios (Table I), were accurately weighed and titrated as above.

RESULTS AND DISCUSSION

Isoniazid and sodium *p*-aminosalicylate, individually, have been titrated with perchloric acid as monoacidic and diacidic bases, using different solvents (9-12). Acetonitrile and acetic anhydride have been found suitable solvents for the titration of bases (13, 14). In the preliminary experiments, both these solvents were tried. The titration curves using acetonitrile as well as acetic anhydride as solvents (Curves *a* and *b* of Fig. 1) indicate two inflections: the first corresponds to sodium *p*-aminosalicylate content and the second indicates the isoniazid end point. It is seen that with acetonitrile, the first inflection is sharply defined while the second inflection point is indistinct (Fig. 1, Curve *a*). On the other hand, the first inflection is somewhat vague but the second inflection stands out quite distinctly in acetic anhydride medium (Fig. 1, Curve *b*).

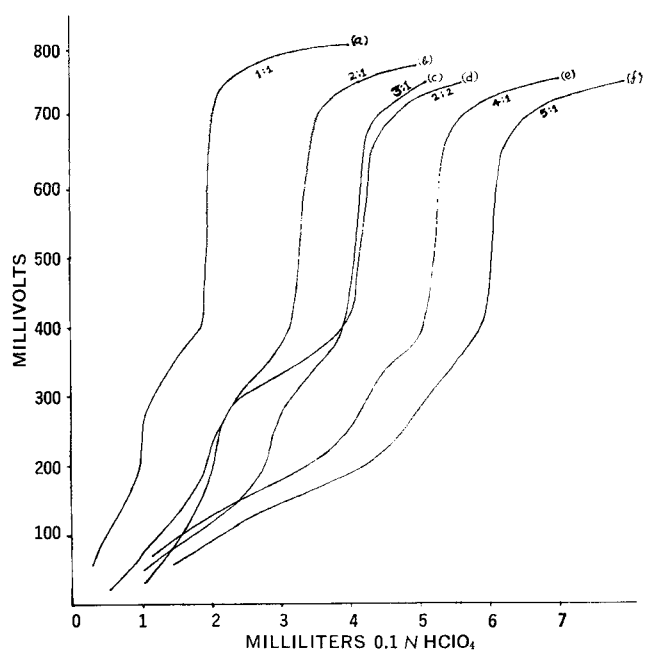


Figure 3—Effect of sodium *p*-aminosalicylate-to-isoniazid ratio on differential titration. The ratios above the curves indicate milliequivalents of sodium *p*-aminosalicylate-isoniazid.

On the basis of these results, mixtures of the two solvents, in varying proportions, were tried as solvent systems. It was seen that while isoniazid-sodium *p*-aminosalicylate (1:1) mixture could be successfully resolved in the solvent mixtures having acetonitrile-acetic anhydride in ratios of 4:1, 2:1, 1:1, 1:2, and 1:3, the solvent mixture in 1:1 was most ideally suited.

Typical titration curves of isoniazid, sodium *p*-aminosalicylate, and isoniazid-sodium *p*-aminosalicylate mixture are shown in Fig. 2. Both the compounds, individually as well as in a mixture, are determined with fair degree of accuracy. Both isoniazid and sodium *p*-aminosalicylate are titrated as monoacidic bases in acetonitrile-acetic anhydride (1:1) mixture.

Since in the usual dosage forms, the amount of sodium *p*-aminosalicylate considerably predominates over the content of isoniazid, the effect of varying the ratio of concentrations of the components on the sensitivity of the differentiating titration was studied. Typical titration curves are shown in Fig. 3 and the recovery of components is recorded in Table I.

Two distinct inflections in the titration curves are obtained when sodium *p*-aminosalicylate-to-isoniazid ratio does not exceed 4 (Fig. 3, Curves *a* to *e*). In the titration of mixtures with ratio of disproportion exceeding 4, only one end point corresponding to the total base is obtained (Fig. 3, Curve *f*). The differential titration of mixtures having sodium *p*-aminosalicylate-to-isoniazid ratio higher than 4:1 was tried employing solvent mixture acetonitrile-acetic anhydride in proportion other than 1:1. The resolution of the end points was not satisfactory.

The proposed procedure makes possible a simple and accurate determination of isoniazid-sodium *p*-aminosalicylate combinations, without preliminary separation of the components. The technique is applicable to those mixtures in which sodium *p*-aminosalicylate-to-isoniazid ratio does not exceed 4.

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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. Isoniazid	Sodium <i>p</i> -Aminosalicylate	Recovery, %	
		Isoniazid ^a	Sodium <i>p</i> -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* acetic 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.