Nonaqueous Titration of Theophylline Combinations with Acetous Perchloric Acid

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Synthetic mixtures of theophylline and sodium acetate, salicylate, and glycinate are titrated with acetous perchloric acid using a potentiometer for the detection of the end points. Differentiation of the equimolecular mixtures could be realized in the solvent mixture containing benzene–acetic anhydride–acetic acid (18:4:1). The method is applied to assay theophylline combinations and their tablets. The results are compared to those obtained by official methods.

IN PHARMACY, various combinations of purines with acetates, salicylates, and glycinates are employed to increase their solubility and effectiveness. Therapeutically, they are extensively used as myocardial stimulants, diuretics, and coronary dilators. Various assay procedures for theophylline in pharmaceuticals have been reviewed (1). In NF, USP, and BP methods, theophylline is precipitated with a silver nitrate solution from an ammoniacal aqueous extract of the preparation; the excess silver nitrate is titrated with a standard solution of ammonium thiocyanate. The method is reported to give erratic results (2). The present investigation was undertaken for devising a simpler method for routine analysis.

Theophylline, being amphoteric, has been titrated both as an acid (3) and as a base (4) in nonaqueous media. Recently, caffeine (5, 6) and theobromine (7) have been estimated as bases in mixtures in water-free media.

In the present report, combinations of theophylline with sodium salts of organic acids are analyzed by differentiating nonaqueous titration. The titration solvent is a mixture of benzene–acetic anhydride–acetic acid (18:4:1), and the titrant is 0.1 *N* acetous perchloric acid. Titration is effected potentiometrically, using a glass-calomel electrode system. The method is applied to assay these combinations in tablet forms. The results by this method compare favorably with those obtained by official methods.

EXPERIMENTAL

Apparatus—All titrations were performed potentiometrically with a pH meter (Polymetron) employing a glass electrode and a calomel electrode with a salt bridge. A saturated solution of lithium chloride in glacial acetic acid formed the bridge.

Reagents and Solutions—Theophylline USP was recrystallized from water and dried at 105°. Sodium acetate BP and sodium salicylate BP were recrystallized from alcohol and dried at 105°. Theophylline sodium acetate NF and theophylline sodium glycinate NF were used without further purification. Theophylline sodium was prepared by mixing theophylline and alcoholic sodium hydroxide (1 *N*) in equimolecular proportions and evaporated to dryness on a water bath. Other chemicals and all solvents used in this study were reagent grade and were employed without further purification. A solvent mixture consisting of 18 parts benzene, 4 parts acetic anhydride, and 1 part acetic acid (benzene–acetic anhydride–acetic acid) was prepared and stored in a reagent bottle. A 0.1 *N* solution of perchloric acid in glacial acetic acid was prepared and allowed to stand 24 hr. prior to standardization against potassium acid phthalate dissolved in glacial acetic acid.

Differentiating Titration of Theophylline and Sodium Salt of an Organic Acid—Approximately 2.0 meq. of each theophylline and sodium salt of an organic acid, accurately weighed, was transferred to a 100-ml. beaker and dissolved by stirring magnetically in 50 ml. of solvent mixture. The solution was titrated potentiometrically with 0.1 *N* acetous perchloric acid. The end points were determined from the inflections of the titration curve obtained by plotting millivolts (mv.) *versus* volume (ml.) of titrant added.

Analysis of Theophylline Sodium Acetate NF—About 50 mg. of the sample, accurately weighed, was dissolved in 50 ml. of the solvent mixture in a 100-ml. beaker. The solution was titrated potentiometrically with 0.1 *N* perchloric acid.

Analysis of Glycine or Sodium Glycinate—About 2.0 meq. of the sample, accurately weighed, was dissolved in a mixture of acetic acid (2.5 ml.) and

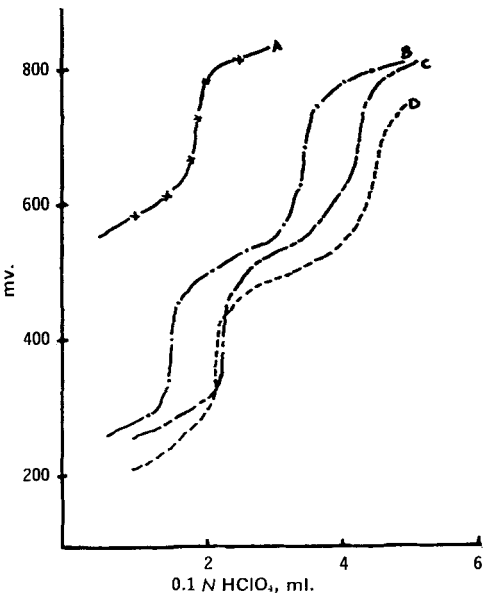

Fig. 1—Typical titration curves of theophylline mixtures against 0.1 N *acetous perchloric acid. Key:* A, *theophylline, 40.5 mg.;* B, *sodium salicylate, 26.7 mg. and theophylline, 41.2 mg.;* C, *sodium acetate, 21.0 mg. and theophylline, 41.2 mg.;* D, *theophylline sodium, 55.8 mg.*

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TABLE I—RECOVERIES OF THEOPHYLLINE AND SODIUM SALT OF ORGANIC ACIDS IN THEIR MIXTURES

Sample	Added, mg.		Found, mg.		Percent Recovery	
	Theophylline	Sodium Salt	Theophylline	Sodium Salt	Theophylline	Sodium Salt
Theophylline and Sodium Acetate (1:1)						
1	41.2	17.5	41.5	17.4	100.7	99.4
2	39.2	16.0	39.4	16.1	100.5	100.6
3	43.0	16.5	42.7	16.4	99.3	99.3
4	41.6	17.2	41.5	17.3	99.7	100.6
Mean					100.0	99.9
SD					0.66	0.73
Theophylline and Sodium Salicylate (1:1)						
1	41.5	30.0	41.7	30.3	100.4	101.0
2	38.0	33.3	37.8	33.1	99.5	99.4
3	40.9	31.5	41.0	31.4	100.2	99.6
4	41.2	32.5	41.0	32.7	99.5	100.6
Mean					99.9	100.1
SD					0.47	0.78
Theophylline and Sodium Glycinate (1:1)[a]						
1	41.7	20.2	41.5	20.1	99.5	99.5
2	41.5	19.5	41.7	19.3	100.4	98.9
3	40.4	18.7	40.4	18.7	100.0	100.0
4	38.7	19.0	38.6	19.1	99.7	100.5
Mean					99.9	99.7
SD					0.39	0.69

[a] Analyzed after treatment with salicylaldehyde.

acetic anhydride (10 ml.) in a 100-ml. beaker by warming on a water bath and allowed to stir for 5 min. Benzene (45 ml.) was added to the solution and titrated as described previously.

Analysis of Theophylline Sodium Glycinate NF—About 50 mg. of the sample, accurately weighed, was dissolved in a mixture of benzene (45 ml.) and acetic acid (2.5 ml.) by warming for 3 to 4 min. on a water bath. Salicylaldehyde (3 ml.) was mixed with it and stirred for 20 min. Acetic anhydride (10 ml.) was then added and the solution was stirred further for 5 min. The titration was carried out as described previously.

RESULTS AND DISCUSSION

The titration of purines in acetic acid against perchloric acid is reported to give unsatisfactory results. However, more distinct end points can be obtained by including acetic anhydride in the solvent mixture (5–8).

In preliminary studies, a series of solvent mixtures containing benzene, chloroform, acetic anhydride, and acetic acid in varying proportions were tested as titration media. Resolution of end points was most satisfactory in a mixture of benzene–acetic anhydride–acetic acid (18:4:1). Typical titration curves are illustrated in Fig. 1.

Curve A of Fig. 1 indicates only one potential break corresponding to theophylline content; whereas two distinct inflections are observed in the titration of theophylline sodium (Fig. 1, Curve D). The first end point corresponds to sodium content and the second to theophylline. Similar potential rises are noted in the titrations of equimolecular mixtures of theophylline-sodium salicylate and theophylline-sodium acetate (Fig. 1, Curves B and C). Both the components of each combination can be estimated with fair accuracy (Table I). The procedure was applied to determine the theophylline content of theophylline sodium acetate NF and its tablets. The difference between the first and second end points corresponds to the amount of theophylline. The results compare favorably with those obtained by NF method (Table II).

Figure 2, Curve E for theophylline sodium glycinate mixture indicates two inflections. The first corresponds to the sodium content and the second to the total basicity of theophylline and glycine. Since the theophylline–glycine mixture could not be differentiated in the solvent mixture used (Fig. 2, Curve B), the glycine was masked with salicylaldehyde. The resulting Schiff's base did not interfere with the titration of theophylline (Fig. 2, Curve D). Equimolecular mixtures of theophylline

TABLE II—ANALYSIS OF PHARMACEUTICAL PRODUCTS CONTAINING THEOPHYLLINE BY DIFFERENT METHODS

Preparations	Labeled Amount	Recovery of Theophylline by	
		NF Method	Proposed Method
Theophylline NF	—	99.8 ± 0.5[a]	100.0 ± 0.4[a]
Theophylline tablet	100 mg./tab.	102.2	101.5
Theophylline sodium acetate NF	—	63.0 ± 0.6[a]	63.1 ± 0.4[a]
Theophylline sodium acetate tablet	100 mg./tab.	61.0	62.2
	200 mg./tab.	120.9	119.7
Theophylline sodium glycinate NF	—	51.3 ± 0.5[a]	51.5 ± 0.6[a]
Theophylline sodium glycinate tablet	150 mg./tab.	76.4	77.5
	200 mg./tab.	102.0	100.6
	300 mg./tab.	150.5	151.6

Figures represent the percent of theophylline, and the standard deviation is calculated from at least five readings.

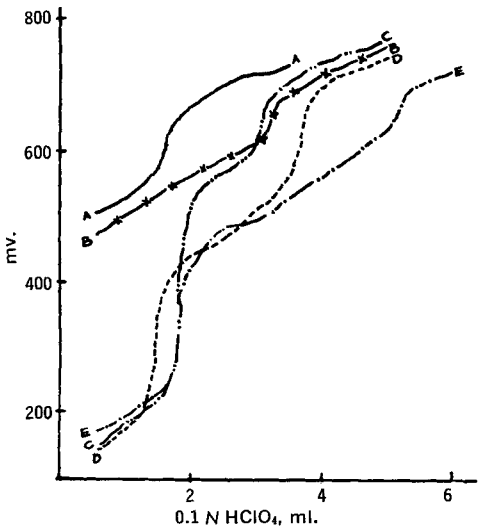

Fig. 2—Titration curves of glycine and its sodium salt individually as well as in combination with theophylline against 0.1 N acetous perchloric acid. Key: A, glycine, 15 mg.; B, glycine, 15 mg. and theophylline, 30 mg.; C, sodium glycinate, 17 mg.; D, sodium glycinate, 17 mg. and theophylline, 40 mg. (with salicylaldehyde treatment); E, sodium glycinate, 17 mg. and theophylline, 40 mg. (without salicylaldehyde treatment).

and sodium glycinate were analyzed by the modified method (Table I). The procedure was applied to determine the theophylline content of theophylline sodium glycinate NF and its tablets. The difference between the first and second end points corresponds to the amount of theophylline present. The results agree closely with those obtained by NF method (Table II).

The usual additives of the tablets except magnesium stearate do not seem to interfere with the determination of theophylline.

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Keyphrases

Theophylline combinations—nonaqueous titrations
Nonaqueous titration—acetous perchloric acid
Potentiometric analysis

Synthesis of Adamantyl Analogs of Analgesics

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The synthesis of adamantyl esters related to heroin, meperidine, and aspirin is reported. Preliminary comparisons in mice indicate the adamantyl ester (V) is more potent and longer acting than meperidine hydrochloride.

THE INCORPORATION of the adamantyl moiety into drugs has been reported to increase the duration of action, and sometimes potency, of the parent compound. For example, 1-(1-adamantyl)-3-(*p*-tolylsulfonyl) urea, the adamantyl analog of tolbutamide, was found to be a very potent and long-acting oral hypoglycemic agent possessing activity two to fifteen times that of tolbutamide (1). The 17β-adamantoate ester of 19-nortestosterone is reported to be much longer acting with little androgenic activity as compared to other esters of the same steroid (2). This increase in duration of action was explained as being due to a decreased rate of enzymatic hydrolysis of the ester, thus making the 17β-hydroxyl group unavailable for biological oxidation to an inactive anabolic agent(2, 3).

In the penicillin series, resistance to penicillinase has been found by experiment to be associated with a side chain derived from a sterically hindered acid. Doyle and Nayler believe that restriction of rotation about the single bond linking the side chain to the amide carbonyl group constrains the molecule to adopt a conformation which is not readily accommodated at the active site of the enzyme (4). Substitution of the usual side chain with various adamantane carboxamide groups provides potent antibiotics that are penicillinase resistant and in some cases are active against Gram-negative bacteria (5–8).

Because of these profound pharmacological effects within different classes of drugs, the authors chose to prepare adamantyl analogs of known analgesics. The proposed compounds were expected to be much

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