The Potentiometric Titration of Aminophylline and Aminophylline-Phenobarbital Mixtures*,†

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The literature is briefly reviewed for methods of determining aminophylline, theophylline, and phenobarbital individually and in combinations with each other. Procedures are presented for potentiometrically titrating phenobarbital, theophylline, and aminophylline; combinations of phenobarbital with either aminophylline or theophylline. Typical titration curves are presented, and the data from several titrations are tabulated. The results obtained by titrating aminophylline potentiometrically are shown to compare favorably with those obtained by the U. S. P. method. The results obtained by potentiometrically titrating mixtures of theophylline and phenobarbital were found to be compatible with the known amounts of these substances present.

THE combining of two or more organic drugs into a single dosage form has complicated the problem of analyzing medicinal preparations. While much progress has been made in this branch of pharmaceutical chemistry in the past few years, a survey of the literature failed to reveal a method for the quantitative determination of aminophylline and phenobarbital combined in tablet form. The evaluation of the methods for assaying these tablet constituents and the results of a preliminary investigation in the search for a more reliable method are the subject matter of this report.

Although the literature does not describe a method for the determination of combinations of aminophylline with phenobarbital in tablets, various methods are reported for the determination of the two compounds individually (1–9). In addition, a method for the determination of combinations of barbiturate and theobromine, an isomer of theophylline, has been reported by Bell (10). The more widely used procedures follow.

Phenobarbital.—The U. S. P. (1) extraction method using a volatile solvent frequently yields high results because of the extraction of impurities which are weighed along with the barbiturate (19).

Among the volumetric methods is the direct titration of the barbituric acid with alkali (6), and a turbidimetric method based on the fact that silver nitrate reacts with phenobarbital in alkaline media to form insoluble silver phenobarbital (7–9, 19).

Mattson and Holt (5) recently modified a colorimetric method developed by Koppanyi and his associates (3, 4), based on the color developed by the reaction of a barbiturate with a cobaltous salt in an alkaline medium. The color reaction of the cobalt-barbiturate complex is not specific and is produced by theophylline and theobromine.

Aminophylline.—Like phenobarbital, the theophylline in aminophylline may be extracted by a suitable solvent from simple preparations and assayed gravimetrically by weighing the residue (11). In a method proposed by Stevens and Wilson (12), and recognized by the U. S. P. (2), theophylline is precipitated as a silver complex with silver nitrate, the excess of that reagent being determined by back-titration. A modification of this method whereby the nitric acid which is quantitatively liberated during the complex formation is titrated with alkali, was proposed by Boie (13) for theobromine, and applied to theophylline by Schulek and Rozsa (14).

Potentiometric Methods.—Potentiometric titration of each of these alkaloids has been reported. Ogston (15), using a calomel electrode and a hydrogen electrode, measured the dissociation constants of methylated xanthines including theophylline. Payne (16) and more recently Waters, Berg, and Lachman (17) reported on the quantitative potentiometric titration of barbiturates with alkali using a glass electrode. Mattocks and Voshall (19) developed a titrimetric procedure whereby a phenobarbital preparation was titrated with silver nitrate, using a silver, silver-silver chloride electrode system.

EXPERIMENTAL

The acidic nature of both substances suggests titration with alkali. While phenobarbital had been titrated with alkali and the end point determined with a suitable indicator (6), no such method was

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found for theophylline. This may be due to the very weakly acid nature of the latter. It was decided to perform a number of potentiometric titrations on: (*a*) pure samples of each compound, and (*b*) mixtures of the two, and to examine the titration curves obtained to determine the feasibility of the method for quantitative determination of the mixed compounds.

The Leeds & Northrup model K-2 potentiometer was used in conjunction with a normal calomel electrode and a smooth platinum electrode.

The titrant was added generally in increments of 0.1 cc. near the end point. After stirring, equilibrium was reached in about fifteen seconds.

The end point was determined from the tabulated data by the method given by Kolthoff and Laitinen (18).

Procedure Used for Phenobarbital.—An accurately weighed sample of approximately 0.07 Gm. of phenobarbital was dissolved with the aid of heat in 150 cc. of distilled water. After cooling, the solution was potentiometrically titrated with 0.1 *N* NaOH.

The curve shown in Fig. 1 is typical for this potentiometric determination. Some of the determinations are summarized in Table I.

TABLE I.—POTENTIOMETRIC TITRATION OF PHENOBARBITAL

Sample Wt.	Alkali *N*	Cc. Used	Wt. Found	%
0.0614	0.0955	2.88	0.0638	104.0
0.0697	0.0955	3.21	0.0712	102.0
0.0795	0.1018	3.37	0.0796	100.0
0.0665	0.1018	2.80	0.0661	99.5

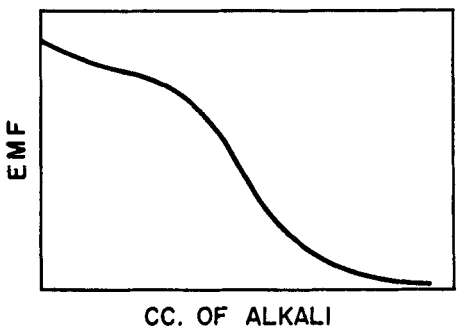

Fig. 1.—Titration curve of phenobarbital.

Procedure Used for Aminophylline.—An accurately weighed sample of approximately 0.12 Gm. of aminophylline was dissolved in 150 cc. of distilled water and potentiometrically titrated with 0.1 *N* NaOH.

The curve shown in Fig. 2 is typical of the potentiometric titration of theophylline in aminophylline. Table II compares several potentiometric determinations with results obtained by the U. S. P. method. The U. S. P. specifies that aminophylline contain from 75 to 82% of anhydrous theophylline. The close agreement between both methods is worthy of notice.

TABLE II.—COMPARISON OF THE U. S. P. AND POTENTIOMETRIC METHODS FOR QUANTITATIVELY ESTIMATING THEOPHYLLINE IN AMINOPHYLLINE

Theophylline Found by the U. S. P. Method (1), %	Theophylline Found by Potentiometric Method, %
1st detn.: 80.40	1st detn.: 80.30
2nd detn.: 80.35	2nd detn.: 80.35

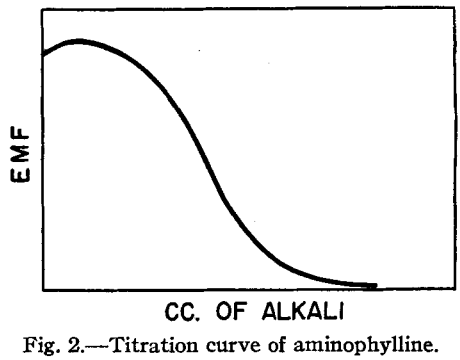

Fig. 2.—Titration curve of aminophylline.

Procedure Used for Aminophylline-Phenobarbital Mixtures.—An accurately weighed sample of approximately 0.07 Gm. of phenobarbital was dissolved in 150 cc. of distilled water with the aid of heat. After cooling, an accurately weighed sample of approximately 0.1 Gm. of aminophylline was dissolved, and the solution potentiometrically titrated with 0.1 *N* NaOH.

Since phenobarbital is more acidic than theophylline, the first end point obtained represents the phenobarbital in the sample. The volume of alkali used by the phenobarbital was subtracted from the total volume indicated by the second end point. This difference represented the volume of alkali needed to neutralize the theophylline. To ascertain the stoichiometric end point of the theophylline, the theophylline content of the aminophylline used as samples was previously determined by the U. S. P. method (2).

The results of several titrations of the mixture are recorded in Table III. The results were not considered entirely satisfactory. The weight of theophylline found was also calculated by using the amount of phenobarbital known to be present, but the same relative deviation persisted.

Procedure Used for Theophylline.—An accurately weighed sample of theophylline was dissolved in 150 cc. of distilled water with the aid of heat. After cooling, the solution was potentiometrically titrated with 0.1 *N* NaOH. Figure 3 is typical of the curve obtained.

Initial determinations of theophylline in water as a solvent were not considered satisfactory. It was observed that results obtained with increased amounts of theophylline were more consistent. An increase in the weight of sample dissolved was made feasible by using alcohol as the solvent. The use of this solvent led to results more readily interpreted than when water alone was used as a solvent.

TABLE III.—POTENTIOMETRIC TITRATION OF AMINOPHYLLINE-PHENOBARBITAL MIXTURES

	Wt. Used	Cc. Used[a]	Wt. Found	%
Phenobarbital	0.0586	2.50	0.0561	96.0
Aminophylline theophylline content	0.1279	...	...	...
	0.1028	5.86	0.1040	101.0
Phenobarbital	0.0588	2.10	0.0471	80.0
Aminophylline theophylline content	0.1364	...	...	...
	0.1096	6.00	0.1045	95.5
Phenobarbital	0.0529	2.35	0.0529	100.0
Aminophylline theophylline content	0.0898	...	...	...
	0.0722	3.88	0.0676	93.5
Phenobarbital	0.0550	2.41	0.0541	98.5
Aminophylline theophylline content	0.1076	...	...	...
	0.0864	4.47	0.0779	90.0

[a] 0.0966 *N* alkali used for each determination.

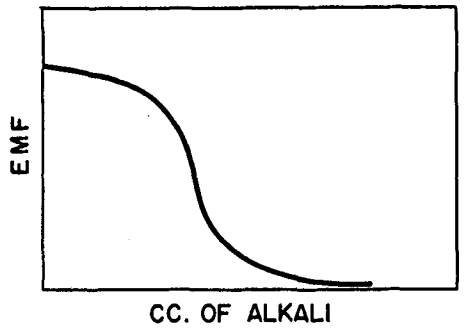

Fig. 3. Titration curve of theophylline.

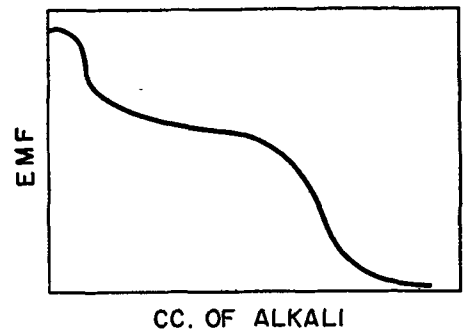

Fig. 4. Titration curve of phenobarbital and theophylline.

TABLE IV.—POTENTIOMETRIC TITRATION OF THEOPHYLLINE-PHENOBARBITAL MIXTURES

	Wt. Used	Cc. Used[a]	Wt. Found	%
Phenobarbital	0.0465	1.92	0.0454	97.5
Theophylline	0.2226	12.19	0.2233	100.5
Phenobarbital	0.0667	2.74	0.0647	97.0
Theophylline	0.1739	9.47	0.1735	100.0
Phenobarbital	0.0664	2.70	0.0638	96.0
Theophylline	0.1713	9.31	0.1706	99.5
Phenobarbital	0.0663	2.71	0.0640	96.5
Theophylline	0.2220	12.16	0.2228	100.5

[a] 0.1018 *N* alkali was used for each determination.

Procedure Used for Theophylline-Phenobarbital Mixtures.—An accurately weighed sample of approximately 0.2 Gm. of theophylline and 0.06 Gm. of phenobarbital was dissolved in 150 cc. of ethyl alcohol and potentiometrically titrated with 0.1 *N* NaOH. A blank was run on the solvent and suitable corrections made.

The curve shown in Fig. 4 is typical of those obtained by titrating the mixture. Table IV summarized the results obtained.

SUMMARY

1. The literature is briefly reviewed for methods of determining aminophylline, theophylline, and phenobarbital individually and in combinations with each other.

2. Procedures are presented for potentiometrically titrating phenobarbital, theophylline and aminophylline; combinations of phenobarbital with either aminophylline or theophylline. Typical curves are presented, and the results of several titrations are tabulated.

3. The results obtained by titrating aminophylline potentiometrically are shown to compare favorably with those obtained by the U. S. P. method.

4. The results obtained by titrating mixtures of theophylline and phenobarbital were found to be compatible with the known amount of these substances present.

Practical applications utilizing the information obtained by this preliminary investigation for commercial mixtures are being studied, and will be reported in a later paper.

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