Determination of Acetylsalicylic Acid and Barbiturate Combinations in Dosage Forms

By SONG-LING LIN* and MARTIN I. BLAKE

A nonaqueous differentiating titrimetric procedure is presented for determining dosage forms containing acetylsalicylic acid and barbiturate combinations. Preliminary extraction of the active components is avoided. The titrant is sodium methoxide in benzene–methanol and the titration solvent is methyl isobutyl ketone. Titrations are effected potentiometrically. An additive procedure is suggested when the ratio of acetylsalicylic acid to barbiturate is greater than 10 to 1. The effect of additives and other active constituents is considered.

THE A.O.A.C. method for the analysis of acetylsalicylic acid and phenobarbital tablets is a spectrophotometric procedure involving preliminary separation of the components on a column of diatomaceous earth[1] which has been treated with dipotassium phosphate. It is based on a procedure developed by Banes (1) for determining phenobarbital in the presence of salicylates, and modified by Byers (2). Although satisfactory results are obtainable by this procedure, it is tedious and time-consuming.

In a previous paper (3) synthetic mixtures of acetylsalicylic acid and a variety of barbiturates were analyzed by a differentiating nonaqueous titration procedure. Titration was effected with a Fisher titrimeter equipped with a glass-calomel or antimony-calomel electrode system. The titration solvent was methyl isobutyl ketone, and the titrant was sodium methoxide in benzene–methanol (10:1). In the present study the method is applied to numerous dosage forms which contain acetylsalicylic acid and barbiturates in addition to additives, excipients, and other active constituents. The dosage form is titrated differentially without preliminary extraction of the active constituents. The effect of interfering substances on the sensitivity of the procedure is considered.

EXPERIMENTAL

Apparatus.—All titrations were performed potentiometrically with a Fisher titrimeter, model 35, equipped with a sleeve-type calomel (Beckman No. 41240) and a glass (Beckman No. 40495) electrode system.

Reagents.—(*a*) Acetylsalicylic acid and all barbiturates were the best quality available from commercial sources and were purified as described in an earlier paper (3). (*b*) Tenth normal sodium methoxide in benzene–methanol (10:1) was prepared and standardized as described by Fritz and Lisicki (4). (*c*) Other chemicals and all solvents used in this study were reagent grade and were employed without further purification. (*d*) Dosage forms were obtained from commercial sources.

General Procedure.—Appropriate amounts of acetylsalicylic acid and phenobarbital, accurately weighed, were transferred to a 150-ml. beaker and dissolved in 70 ml. of methyl isobutyl ketone with the aid of magnetic stirring. The solution was titrated potentiometrically with 0.1 *N* sodium methoxide in benzene–methanol (10:1), using a glass-calomel electrode system. The end points were determined from the inflections of the titration curve obtained by plotting millivolts (mv.) *versus* volume (ml.) of titrant added. During the titration process, the titration beaker was covered with a rubber plate having holes for the passage of the electrodes and the buret tip.

Effect of Other Ingredients on Differentiating Titration.—Approximately 0.60 meq. of acetylsalicylic acid, 0.40 meq. of phenobarbital, and an amount of other active constituents as indicated in Table II, accurately weighed, were dissolved in 70 ml. of methyl isobutyl ketone. The titration and end point detection were carried out as previously described.

Application of Additive Method.—Twenty tablets were weighed and powdered. An aliquot of the powder mass equivalent to about 0.90 meq. of acetylsalicylic acid was accurately weighed and transferred to a 150-ml. beaker. Amounts of pure phenobarbital, accurately weighed, were added to aliquots of the powder mass to bring the phenobarbital content from 0.07 meq. to a maximum of 0.35 meq. The samples were then dissolved in 70 ml. of methyl isobutyl ketone, and the solutions were titrated as described previously.

Analysis of Dosage Forms.—Seven dosage forms containing acetylsalicylic acid, a barbiturate, and other active ingredients were analyzed for their content of both acetylsalicylic acid and barbiturate by differentiating nonaqueous titration. Twenty tablets were weighed and powdered, or 20 capsules were emptied as completely as possible and the

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* Present address: Pharmacy Research and Development Division, Ciba Pharmaceutical Co., Summit, N.J.

[1] Marketed as Celite 545 by the Johns-Manville Corp., New York, N. Y.

contents weighed. A sample of the powder mass equivalent to about 0.85 meq. of acetylsalicylic acid was accurately weighed and transferred to a 150-ml. beaker. The sample was dissolved in 70 ml. of methyl isobutyl ketone. When the additive method was employed, sufficient pure barbiturate powder was accurately weighed and added to the powder mass to make the ratio of acetylsalicylic acid-to-barbiturate more favorable for differentiating titration. The sample was then dissolved in 70 ml. of methyl isobutyl ketone. The direct titration procedure and the additive modification were applied to each dosage form. End points were determined as described previously.

Table I.—Differentiating Titration of Acetylsalicylic Acid and Phenobarbital

Amt. Weighed, Gm.		Recovery, %	
Acetylsalicylic Acid	Phenobarbital	Acetylsalicylic Acid	Phenobarbital
0.1942	0.2488	100.72	98.79
0.1908	0.2038	100.09	99.10
0.1832	0.2149	100.02	99.75
0.1810	0.1936	100.54	100.12
0.1777	0.2008	98.32	100.58
0.1546	0.1832	99.65	99.30
0.1433	0.1992	100.42	100.05
0.1268	0.1662	99.89	100.00
0.1092	0.1190	99.90	100.38
0.0901	0.1224	100.06	98.96
	Av.	99.96	99.70
	S.D.	±0.67	±0.63

RESULTS AND DISCUSSION

Differentiating nonaqueous titrimetry has provided a simple and useful technique for determining mixtures of acids (or bases) in dosage forms. The acids (or bases) in the mixture must differ significantly in their ionization constants, interfering substances must be absent, and the proper selection of titrant, titration solvent, and electrode system must be made. When these conditions have been met, complex dosage forms can be assayed by a single titration and preliminary treatment of the sample is unnecessary. Time-consuming and involved extraction procedures are avoided.

In an earlier paper (5) the differentiating titration of the weak bases acetophenetidin and caffeine in APC dosage forms was reported. The titrant was perchloric acid in acetic acid–acetic anhydride (1:1) and the titration solvent was acetic anhydride–chloroform–benzene (1:1:9). The differentiating

Table II.—Effect of Other Active Constituents on Differentiating Titration of Acetylsalicylic Acid and Phenobarbital

Active Constituent Added[a]	Amt. Weighed, mg.	Recovery, %	
		Acetylsalicylic Acid	Phenobarbital
Acetophenetidin	90	99.85 ± 0.63[b]	100.06 ± 0.49
Caffeine	50	99.67 ± 0.50	98.65 ± 0.62
Acetophenetidin	90	100.46 ± 0.48	100.16 ± 0.72
Caffeine	45		
Dextroamphetamine sulfate	10	99.62 ± 0.56	99.41 ± 0.84
Dextroamphetamine sulfate	40	99.76 ± 0.67	99.68 ± 0.52
Acetophenetidin	90		
Dextroamphetamine sulfate	10	100.16 ± 0.82	99.98 ± 0.60
Hyoscyamine sulfate	10	99.60 ± 0.70	99.00 ± 0.50
Hyoscyamine sulfate	30	100.06 ± 0.82	98.86 ± 0.76
Acetophenetidin	90		
Hyoscyamine sulfate	5	100.64 ± 0.65	100.82 ± 0.86

[a] Active constituents added in addition to acetylsalicylic acid and phenobarbital. [b] Standard deviation is based on at least 4 determinations.

Table III.—Application of Additive Method to the Determination of a Dosage Form Containing Acetylsalicylic Acid and Phenobarbital

Curve Ref.[a]	Aliquot of Tablet Mass Weighed, meq.		Pure Phenobarbital Added, meq.	% Label Claim Found	
	Acetylsalicylic Acid	Phenobarbital		Acetylsalicylic Acid	Phenobarbital
A	0.90	0.07	0.00	One End Point[b]	
B	0.90	0.07	0.07	98.92 ± 0.62[c]	100.06 ± 0.50
C	0.90	0.07	0.14	100.41 ± 0.51	99.69 ± 0.43
D	0.90	0.07	0.21	100.27 ± 0.35	99.77 ± 0.28
E	0.90	0.07	0.28	100.34 ± 0.46	100.04 ± 0.38

[a] The letter corresponds to those in Fig. 1. [b] Corresponds to acetylsalicylic acid plus phenobarbital. [c] Standard deviation is based on at least 4 determinations.

TABLE IV.—COMPARATIVE STUDY OF DIRECT AND ADDITIVE PROCEDURES FOR THE ANALYSIS OF DOSAGE FORMS CONTAINING ACETYLSALICYLIC ACID AND BARBITURATE

Dosage Form	Active Ingredients Labeled Amt.[a]	% Label Claim Found—Direct Titration: Acetylsalicylic Acid	Direct Titration: Barbiturate	Additive Method: Acetylsalicylic Acid	Additive Method: Barbiturate
Capsule A	Acetylsalicylic acid, 5 gr. Amobarbital, 3/4 gr.	100.80 ± 0.47[b]	98.63 ± 0.65	101.38 ± 0.36	99.88 ± 0.48
Capsule B	Acetylsalicylic acid, 3 gr. Allylisobutylbarbituric acid, 3/4 gr. Acetophenetidin, 2 gr. Caffeine, 2/3 gr.	101.68 ± 0.39	99.09 ± 0.72	98.32 ± 0.52	100.48 ± 0.81
Tablet A	As in capsule B	100.39 ± 0.45	98.87 ± 0.62	99.93 ± 0.48	98.72 ± 0.57
Yellow Tablet B	Acetylsalicylic acid, 2.5 gr. Amobarbital, 1/2 gr. Acetophenetidin, 2.5 gr. Dextroamphetamine sulfate, 5 mg.	98.53 ± 0.81	100.71 ± 0.91	99.31 ± 0.67	99.82 ± 0.51
Yellow Tablet C	Acetylsalicylic acid, 3.5 gr. Phenobarbital, 1/4 gr. Acetophenetidin, 2.5 gr.	One end point[c]		98.27 ± 0.85	99.37 ± 0.38
Gray Tablet D	Acetylsalicylic acid, 2.5 gr. Phenobarbital, 1/4 gr. Acetophenetidin, 3 gr. Hyoscyamine sulfate, 0.031 mg.	One end point		98.86 ± 0.76	100.39 ± 0.60
Capsule C	As in gray tablet D	One end point		100.42 ± 0.28	98.83 ± 0.46

[a] Per unit dosage form. [b] Standard deviation is based on at least 4 determinations. [c] Corresponds to aspirin plus barbiturate involved.

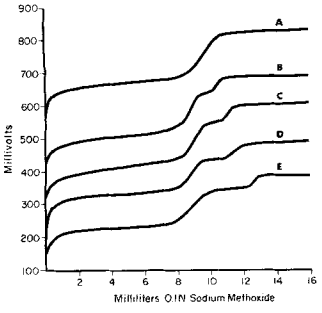

Fig. 1.—Titration curves for differentiating titration of acetylsalicylic acid and phenobarbital in dosage forms by additive method. Data are shown in Table III.

titration of synthetic mixtures of acetylsalicylic acid and barbiturates has been reported (3). The titration solvent was methyl isobutyl ketone and sodium methoxide in benzene–methanol was the titrant. In the present study this procedure has been applied to complex dosage forms containing acetylsalicylic acid and a variety of barbiturates in addition to certain additives, excipients, and other active constituents.

A series of 10 samples of a synthetic mixture of acetylsalicylic acid and phenobarbital was analyzed by the proposed method. The data in Table I indicate the accuracy and precision obtainable by the procedure.

Since acetylsalicylic acid and barbiturates are frequently combined with other therapeutic agents, the effect of these agents on the differentiating titration was studied. The constituents listed in Table II were added individually to a mixture of acetylsalicylic acid and phenobarbital and the combination was titrated by a differentiating titration. The content of the added active component was roughly that which is found in commercial dosage forms. It is apparent from the data in Table II that the added constituents do not interfere in the proposed assay pressured. In general, basic compounds and salts will not interfere. Acids comparable in strength to acetylsalicylic acid or phenobarbital will interfere with the titration. One of the commercial dosage forms procured for this study contained ascorbic acid in addition to acetylsalicylic acid and phenobarbital. A differentiating titration was not successful in this case.

The effect of disproportionate concentrations of acetylsalicylic acid to barbiturate on the differentiating titration was reported in an earlier paper (3). In synthetic mixtures when the acetylsalicylic acid-to-phenobarbital ratio was as high as 10:1, differentiation was not possible. Only one end point corresponding to the total acid present was obtained. An additive method is therefore proposed in which an amount of pure barbiturate is added to the powder mass to assure a ratio more favorable for differentiation. A similar technique (5) was shown to be useful in the differentiation of acetophenetidin and caffeine in APC combinations where dosage forms usually contain the components in the ratio of about 5:1. Dosage forms customarily (Table IV) contain a significantly greater proportion of acetylsalicylic acid than barbiturate. The applicability of the additive procedure was therefore tested on a typical dosage form. The data are reported in Table III. The ratio of the components in the dosage form was 13:1. By the direct titration method (no added phenobarbital) only one end point, corresponding to total acid present, was obtained. With the additive method the ratio of components was varied from 6.4:1 to 2.6:1. In each case differentiation was realized. Typical titration curves are shown in Fig. 1. Curves B through D show two distinct inflections, the first corresponding to the acetylsalicylic acid, and the second representing the barbiturate end point. Quantitative recoveries for both components are recorded in Table III.

Seven commercially available dosage forms were analyzed by the proposed assay using both the direct method and the additive modification. The results of the analyses are reported in Table IV. When the acetylsalicylic acid-to-barbiturate ratio is below 10:1, the direct method is suitable. For those dosage forms having a ratio of 10 or greater, the additive method must be applied.

The weak bases, caffeine and acetophenetidin, and the salt, amphetamine sulfate, did not interfere in the proposed assay. The excipients, coloring agents, diluents, and fillers employed in the formulation of the dosage forms apparently do not interfere. While these agents may suggest a possible source of difficulty in the titrimetric analysis of dosage forms, it has been shown by Chatten and Mainville (6) that in fact these agents do not represent an important source of interference even when the agents themselves are titratable.

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Neutralization of Aluminum Hydroxide Dried Gel

Citrate and Tartrate Inhibition

By MILO GIBALDI and DANIEL MUFSON

Studies were conducted on the neutralization rate of aluminum hydroxide dried gel (AHDG) with HCl as a function of rate of agitation and amount of AHDG. On the basis of these studies it is suggested that the AHDG–HCl neutralization reaction is chemically controlled. Sodium citrate and tartrate were tested as inhibitors of AHDG. Their effect on the neutralization rate was investigated by neutralization, sedimentation, and complexation studies. It was concluded that a dual mechanism is operative to produce inhibition; the AHDG reacts with the salt to produce protons, and this effect, coupled with flocculation, causes a retardation in the rate of change of pH with time.

DESAI *et al.* (1), in 1963, employing the "buffering capacity" procedure, found extensive inhibition of the antacid activity of a large number of commercial antacid products when polypeptides were added to artificial gastric juice. The polypeptides had no effect on the time required to terminate the procedure, but greatly reduced the maximum pH attained. Products containing AHDG were most sensitive to this inhibitory effect.

Gibaldi and co-workers (2) found that the effect of polypeptides on "buffering capacity" could be ascribed to an inhibitory influence on the rate of neutralization. They, therefore, proposed that neutralization rate studies would be as indicative of the activity of a given antacid under different experimental conditions as the more elaborate "buffering capacity" experiments. These workers found that the neutralization rate is strongly dependent on the amount of aluminum hydroxide dried gel (AHDG) employed as well as the amount of inhibiting agent. Inhibition of activity was noted with various proteins, polypeptides, and amino acids. In addition, inhibition was found in the presence of acetate and citrate. Neither of these materials had a perceptible effect on the initial pH of the test solution or on the equilibrium pH. Two possible explanations for the observed inhibition effects, *viz.*, the formation of an *insoluble* AHDG–inhibitor complex and the adsorption of the inhibitor on the surface of the dispersed AHDG particles, were ruled out by the results of their investigations. The authors suggested the formation of a *soluble* complex between AHDG and the inhibitors tested.

In 1933, Tartar *et al.* (3) studied the influence of adsorbed ions on the dissolution of colloidal aluminum hydroxide in HCl. Aluminum hydroxide was allowed to dissolve in HCl in the presence of various salts. The solubility of aluminum hydroxide was determined at the end of 24 hr. at 25°. The data indicated that the greater the concentration of electrolyte, such as arsenate, phosphate, or sulfate, the greater the amount of aluminum hydroxide dissolved.

These authors noted that the "speed" (24-hr. solubility) of the reaction between colloidal aluminum hydoxide and 0.2 *N* hydrochloric acid is increased several-fold by the presence of electrolytes yielding anions of higher valence. It should be pointed out, however, that these workers did not clearly show that the test electrolytes increased the velocity of dissolution since only apparent equilibrium solubility was measured. They proposed that their findings were attributable to the ability of the anions of higher valence to modify the speed of the reaction by influencing the electrical potential at the solid-liquid interface. Tarter (3) also presented evidence which indicated that the change in the "speed" of the reaction was not due to an increase in the surface

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