Comparison of Methods for the Determination of Salicylic Acid in Buffered Aspirin Tablets

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Abstract ☐ New procedures are described for the determination of the free salicylic acid content and the total nonaspirin salicylate content of buffered aspirin tablets. Free salicylic acid and total nonaspirin salicylate contents of a number of tablet samples were determined. The new procedure for nonaspirin salicylates yielded results which were in close agreement with those found using the Levine and Weber method. No relationship was found between the free salicylic acid content and the total nonaspirin salicylate content of buffered tablets. The USP XVII test method for free salicylic acid yielded results which were consistently and significantly lower than those found with the other methods studied.

Keyphrases ☐ Salicylic acid analysis—buffered tablets ☐ Buffered aspirin tablets—assay methods comparison ☐ Citric acid procedure —free salicylic acid determination ☐ Column chromatography— separation ☐ UV spectrophotometry—analysis

A previous publication (1) was concerned with two problems which can be encountered in the determination of free salicylic acid in buffered aspirin products. It was shown that adsorption of acid by buffering components can occur and that chloroform-insoluble buffering agents can catalyze a conversion of aspirin, in chloroformic solution, to a compound which is determined as salicylic acid. It was found that treatment of a sample with citric acid monohydrate markedly inhibited both processes and the analytical implications of such a treatment were discussed.

An additional problem has been recognized as important in the determination of salicylic acid in buffered products and arises from the fact that salicylic acid produced by hydrolysis of aspirin can exist in tablets in the form of free acid and as chloroform-insoluble salts. A mechanism which can explain the formation of such salts in tablets was recently described by Kornblum and Zoglio (2). Although it has been recognized for some time that the free salicylic acid test method described for buffered aspirin tablets in the 17th revision of the "United States Pharmacopeia" does not respond to chloroform-insoluble salts of salicylic acid (3), only recently has a method for the determination of total nonaspirin salicylates in such products been described in the literature by Levine and Weber (4). This method exposes a sample to an initial formic acid treatment which apparently results in displacement of salicylic acid from its salts and additionally modifies the surface characteristics of the buffers so that adsorption no longer occurs. Details of this procedure were kindly provided to this laboratory, prior to publication, by the authors and this communication reports on a comparative study of the USP test method, the Levine and Weber method, and an alternative method developed in these laboratories.

The Levine and Weber method was evaluated using three different brands of commercially available buffered aspirin tablets. The method appeared to work well and the precision of the method was good. It was, however, thought desirable to develop an alternative procedure in order to assess the accuracy of the method. An obvious approach to the problem of converting salts of salicylic acid to the chloroform-soluble free acid is to treat the residue after chloroform extraction of powdered sample with strong acid, and to extract the aqueous solution so obtained with additional chloroform. This approach was not successful when applied to synthetic mixtures and yielded results which were much higher than theory. It was concluded that high recoveries resulted from aspirin degradation in chloroform during the time period required for sample dissolution and from adsorption of aspirin to solids which subsequently hydrolyzed during the strong acid treatment. In view of this, advantage was taken of the previously reported observation that treatment of powdered buffered tablets with citric acid monohydrate resulted in a modification of the chloroform-insoluble solids so that adsorptive and catalytic properties were markedly reduced. The method essentially consists of treating, by trituration, a powdered sample with an equal weight of citric acid monohydrate, dissolving out aspirin and free salicylic acid from the powder mass with chloroform, treating the resulting residue with an aqueous solution of a strong acid, and extracting the resulting solution with chloroform. The two chloroform extracts are combined and the salicylic acid content is determined by the chromatographic method of Weber and Levine (5). With the assumption that the citric acid treatment results only in desorption of salicylic acid and aspirin and does not cause conversion of salicylic acid salts to free acid (1), a method is also available for the estimation of the free salicylic acid content as well as total nonaspirin salicylate contents of buffered tablets.

EXPERIMENTAL

Materials—Chloroform, ether, and glacial acetic acid were of reagent grade.[1] The buffered aspirin tablets were obtained from local pharmacies.

Procedures—The USP procedure was that described in the 17th revision of the "United States Pharmacopeia" under "Free salicylic acid" in the Aspirin Tablets monograph for tablets which are coated or contain buffers (6).

The method of Levine and Weber was that described in the literature (4).

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[1] From Fisher Scientific Co., Pittsburgh, Pa.

Table I—Results Obtained when Various Methods Were Employed to Estimate Salicylic Acid (SA) Contents of a Number of Commercial Buffered Aspirin Products

Product	Buffers Present	USP Procedure	% SA Found Using		
			Citric Acid Procedure for Free Salicylic Acid	Levine and Weber Procedure	Citric Acid Procedure for Total Nonaspirin Salicylates
L.	Aluminum hydroxide	2.19	4.02	6.59	6.64
	Magnesium hydroxide	2.80	4.02	6.53	6.58
		3.03	3.89		6.62
					6.79
B.	Aluminum glycinate	Not detectable	0.211	0.64	0.728
	Magnesium carbonate		0.236	0.69	0.718
			0.219	0.62	0.739
				0.67	
R.	Aluminum hydroxide	0.455	1.01	3.79	3.78
	Glycine			3.91	3.58
	Magnesium carbonate			3.52	3.58
A. S.	Calcium phosphate Sodium bicarbonate Citric acid	—	5.22	—	5.92
M.	Aluminum hydroxide Glycine Magnesium carbonate	—	0.682	—	2.81
A.	Aluminum hydroxide Magnesium hydroxide	—	1.82	—	3.39
G.	Calcium carbonate Magnesium carbonate	—	1.96	—	3.37

Citric Acid Procedure for Free Salicylic Acid—Place an accurately weighed portion of powdered buffered aspirin tablets equivalent to 400 mg. of aspirin in a glass mortar. Add an equal weight of citric acid monohydrate and thoroughly mix by trituration with a glass pestle. Add 20 ml. of chloroform and stir for approximately 15 min. Filter the mixture and collect the filtrate in a 50-ml. volumetric flask. Wash the mortar and pestle with two 10-ml. portions of chloroform and pass the washings through the filter and collect in the volumetric flask. Add chloroform to volume. Pipet an appropriate volume of the resulting solution into a chromatographic column prepared by packing the mixture obtained when 3 g. of diatomaceous earth[2] is hydrated with 2 ml. of ferric chloride–urea reagent (6). Pass 50 ml. of chloroform through the column, rinse the tip of the chromatographic tube with chloroform, and discard the eluate. Elute the adsorbed salicylic acid into a 50-ml. volumetric flask containing 10 ml. of methanol and 2 drops of hydrochloric acid by passing 10 ml. of a 1 in 10 solution of glacial acetic acid in ether (use water-saturated ether) and then 30 ml. of chloroform through the column. Dilute the eluate with chloroform to volume. Determine the absorbance of the solution at a wavelength of 306 mμ against a solvent blank of the same composition as the sample solvent using a suitable spectrophotometer. Determine the concentration of salicylic acid in the solution by comparing the absorbance to that obtained at the same wavelength with a solution of salicylic acid at a concentration of 25 mcg./ml. in the same solvent system.

Citric Acid Procedure for Total Nonaspirin Salicylates—Place an accurately weighed quantity of powdered buffered aspirin tablets, equivalent to 500 mg. of aspirin in a glass mortar, add an equal weight of citric acid monohydrate, and thoroughly mix by trituration with a glass pestle. Add 40 ml. of chloroform and stir for about 15 min. Filter the mixture and collect the filtrate in a 200-ml. volumetric flask. Wash the mortar and pestle with two 20-ml. portions of chloroform, pass the washings through the filter, and collect in the volumetric flask. Transfer the residue obtained in the filtration step to a 125-ml. separator containing 10 ml. of 1 N hydrochloric acid. After effervescence has ceased, add 25 ml. of chloroform and shake. Drain the chloroform layer into the volumetric flask. Repeat the extraction with 3 additional portions of chloroform, draining each portion into the volumetric flask. Add chloroform to volume and mix. Proceed as described in the citric acid procedure for free salicylic acid beginning with the phrase "Pipet an appropriate volume of the resulting solution. . . ."

RESULTS AND DISCUSSION

The results of studies on a number of buffered aspirin tablet products are summarized in Table I. Inspection of the table makes obvious that the salicylic acid contents as determined by the USP procedure were consistently and significantly lower than those determined by the other methods. It is logical to assume that these low values resulted from adsorption of significant amounts of salicylic acid during sample workup and to the insensitivity of this procedure to salicylic acid which is present in the sample in the form of salts. There is good agreement between results obtained with the Levine and Weber method and the citric acid procedure for total nonaspirin salicylate content. The methods appear to be equally precise. The citric acid procedure was found in these laboratories to be somewhat more convenient since it utilized a single-column chromatographic step rather than the two necessary in the Levine and Weber method. There is a possible hazard that, with the former procedure, some aspirin might remain in the residue and be converted to salicylic acid by the strong acid treatment. That this is not a real hazard is supported by the close agreement between the results obtained with the two different methods. Furthermore, even if adsorption of aspirin were not completely inhibited by citric acid treatment, little hydrolysis would be expected in view of the low concentration of aspirin that would be present in solutions prepared by acidifying a residue, and the relatively short time required for acidification and extraction. It is interesting to observe the difference obtained between the two different citric acid procedures. The differences reflect the fact that significant amounts of salicylic acid can be present in buffered tablets as chloroform-insoluble salts. It is also apparent that no relationship exists between the free salicylic acid content and total nonaspirin salicylate content of the tablets.

Perhaps the most surprising result of this study is the revelation of the very high nonaspirin salicylate content of most of the products examined. Only two of the seven products studied met the existing officially recognized limit of 0.75 % for free salicylic acid. Only one product would pass the limit test if the limit was intended to reflect all nonaspirin salicylates.

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[2] Celite 545, Johns-Manville, New York, N. Y.

(3) F. A. Morecombe, private communication.

(4) J. Levine and J. D. Weber, *J. Pharm. Sci.*, **57**, 631(1968).

(5) *Ibid.*, **55**, 78(1966).

(6) "United States Pharmacopeia," 17th rev., Mack Publishing Company, Easton, Pa., 1965, p. 51.

Polarographic Assay of Glyceryl Trinitrate Sublingual Tablets for Content Uniformity

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Abstract ☐ A polarographic method of assaying glyceryl trinitrate in sublingual tablets is presented. The method is direct, rapid, and free from interference by nitrate and nitrite ions. Its sensitivity is sufficient to permit the analysis of single tablets with a precision of ±1%. Polarographic analysis of pharmaceutical preparations gives results comparable to but more precise than those obtained by the current BP and USP methods.

Keyphrases ☐ Glyceryl trinitrate sublingual tablets—analytic method ☐ Polarography—analysis ☐ Analyses, comparison—glyceryl trinitrate tablets ☐ Colorimetric analysis—spectrophotometer ☐ IR spectrophotometry—analysis

Current methods of assaying glyceryl trinitrate in pharmaceutical preparations are based on the following techniques: reduction of nitrogen to ammonia determined subsequently by titration (1); IR spectrophotometry (2); acid hydrolysis to nitrate ion and subsequent spectrophotometric determination of nitrated phenoldisulfonic acid (3); and alkaline hydrolysis to nitrite ion followed by diazotization and spectrophotometric determination (4). The first two techniques require 5 mg. of glyceryl trinitrate per determination and hence are unsuitable for the analysis of single sublingual tablets, which usually contain 0.3–0.6 mg. of drug. The nitration method is indirect and subject to interference from nitrate ion. The diazotization method is likewise indirect, and subject to interference from nitrite ion.

In order to overcome these shortcomings, a polarographic method was developed. The reduction of nitrate esters at the dropping mercury electrode has been studied by several authors (5–7). In aqueous ethanolic solution a well-developed single wave, independent of pH in the range of 3 to 13, was observed. The products of the reduction were the parent alcohol and nitrite ion. It was deduced that the reduction was diffusion-controlled and irreversible with two electrons being consumed with each nitrate group.

EXPERIMENTAL

Reference Standard—USP glyceryl trinitrate reference standard was used. Each 100 mg. of standard was labeled to contain 9.25 mg. of glyceryl trinitrate in a diluent of lactose.

Polarographic Solvent—Eight hundred milliliters of 2-propanol was mixed with 100 ml. of 1.0 N tetramethylammonium chloride and 100 ml. alkaline buffer (0.10 N in NH_4Cl and NH_4OH). The polarogram of the solvent, recorded daily under conditions analogous to those of the samples, was examined for waves due to impurities. This polarogram subsequently served as the blank (Fig. 1).

Apparatus—A polarograph[1] with synchronous drop controller[2] was used for all polarographic determinations. Measurements of potential were obtained with a silver/silver chloride electrode and then expressed relative to the saturated calomel electrode (8). The solution in the salt bridge was replaced daily. Unless otherwise noted, the following polarographic parameters were used: drop time, 0.2 sec; temperature, 34.8 ± 0.1°; scan speed, 0.4 v./min.; scan range, 0.0 to −2.0 v.; sensitivity, 5 × 10^{-8} A/mm.; and damping, nil. Currents were measured at the midpoint of the oscillations.

A spectrophotometer[3] was used to measure absorbance in the visible range. A spectrometer[4] was used in the IR range. A conductivity bridge[5] was used to determine conductivities and a meter[6] to obtain pH measurements.

Method of Assay—*Single Tablets*—Place a tablet into the polarographic cell and powder carefully with a glass rod. Add 10.0 ml. of solvent for each 0.6 mg. of glyceryl trinitrate. Thoroughly mix for 30 sec. Remove the glass rod, add a small magnetic stirring bar, and couple the cell to the polarograph. Deoxygenate the sample mixture with pure nitrogen (saturated at room temperature with solvent) while stirring for a period of 25 min. (Stirring must be sufficiently vigorous to maintain the solid phase in motion.) Record the polarogram from 0.0 to −2.0 v.

Transfer an accurately weighed quantity of the reference standard equivalent to approximately 6 mg. of glyceryl trinitrate to a 100-ml. volumetric flask. Make up to volume with solvent, add a magnetic stirring bar, and agitate (with occasional inversion) for 20 min. Transfer an aliquot (of the same volume as that used for the analysis of the sample) to the polarographic cell, add a small stirring bar, and

[1] Metrohm model E261, Herisou, Switzerland.
[2] Metrohm model E354.
[3] Beckman model DU-2, Beckman Instruments, Inc., Fullerton, Calif.
[4] Perkin-Elmer model 221, Norwalk, Conn.
[5] Industrial Instruments model RC-16B, Beckman Instruments, Inc.
[6] Metrohm model E300.