Rapid Simultaneous Determination of Salicylic Acid and Aspirin by GC I: Analysis of Synthetic Aspirin–Salicylic Acid Mixtures and of Single-Component Aspirin Tablets

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Abstract □ A rapid, sensitive GC method for the simultaneous analysis of salicylic acid and aspirin in admixtures and in single-component acetylsalicylic acid (aspirin) tablets is presented. The procedure involves conversion of the two drugs to their methyl esters with diazomethane in tetrahydrofuran solution and subsequent isothermal elution of the components from a 5% OV-210 on Diatoport S glass column. Quantitation is effected by means of an electronic digital integrator with methyl *o*-methoxybenzoate as the internal standard. The average total drug recovery of 16 synthetic mixtures was 99.70%, with a standard deviation of ±0.58%, while the mean total recovery using the USP procedure was 99.40 ± 0.68%. When applied to the analysis of commercial single-component compressed and enteric coated aspirin tablets, the proposed technique gave results which were, in the majority of cases, in excellent agreement with the USP values for both aspirin and salicylic acid content. With a few formulations, the salicylic acid content was found to be slightly higher with the GC procedure than with the method described in the USP.

Keyphrases □ Salicylic, acetylsalicylic acids—simultaneous determination □ Aspirin tablets—analysis □ GC—analysis □ Methyl *o*-methoxybenzoate—internal standard, GC

In recent years, the drug field has witnessed the proliferation of methods for the analysis of salicylic acid and acetylsalicylic acid (aspirin) in pharmaceuticals and in various biological media. Surprisingly few, however, have been developed expressly for their simultaneous determination, and most require a separation step prior to quantitation of the individual components.

In the USP (1) and in the work of Levine and Weber (2, 3), the salicylic acid is trapped as a complex on a ferric chloride–urea–siliceous earth column prior to elution and subsequent spectrophotometric measurement. A second aliquot is then employed for the estimation of the aspirin. The BP (4) monograph for aspirin includes a limit colorimetric test for salicylic acid and an aqueous residual titration procedure for aspirin. Lin (5) differentiated the two drugs in synthetic mixtures by nonaqueous potentiometric titration, but this method would not appear to be sufficiently sensitive for the analysis of salicylic acid at the low levels normally encountered in aspirin raw material and commercial dosage forms. Lee *et al.* (6) reported a quantitative separation by Sephadex gel filtration and spectrophotofluorometric measurement of the column effluent but gave no data on the recoveries of the components. More recently, Shane and Miele (7) and Miles and Schenk (8) described rapid fluorometric methods for the determination of salicylic acid and aspirin in aspirin products. Several GC procedures have been proposed for the estimation of aspirin and/or salicylic acid as the free acids (9) or after derivatization to the trimethylsilyl (10) or methyl esters (11), but these methods either do not involve simultaneous measurement or otherwise present no supporting data for the quantitation of salicylic acid.

In this paper, a rapid, sensitive GC method for the simultaneous analysis of salicylic acid and aspirin in admixtures and in single-component aspirin tablets is presented. The drugs are converted to their methyl esters with diazomethane prepared in tetrahydrofuran solution and are eluted isothermally from a 5% OV-210 on Diatoport S system contained in a glass column. Peak areas are accurately measured with a printout digital electronic integrator, with methyl *o*-methoxybenzoate as the internal standard. The results are compared for precision and accuracy against those obtained with the USP method, and the merits of the proposed procedure are evaluated.

EXPERIMENTAL

Preparation of Diazomethane—*Materials*—The following were used: (*a*) tetrahydrofuran, B.D.H. reagent grade; (*b*) 2-(2-ethoxyethoxy)ethanol (Carbitol), Baker grade; and (*c*) *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide, Baker grade.

Procedure—The method selected for the preparation of diazomethane was essentially that of Deboer and Backer (12) but was scaled down 10-fold and employed tetrahydrofuran instead of diethyl ether. The apparatus was also modified to consist of a 50-ml. distilling flask with a side arm bent so as to fit through a cork stopper into a 50-ml. receiving conical flask. Through a second hole in the stopper was inserted a U-shaped outlet tube passing into and below the surface of tetrahydrofuran (4 ml.) contained in a second unstoppered conical flask. Both receiving flasks were cooled in an ice–salt mixture.

The solution of *N*-methyl-*N*-nitroso-*p*-toluenesulfonamide (4.3 g.) in tetrahydrofuran (25 ml.) was added dropwise over 60–75 min. through a 60-ml. long-stemmed dropping funnel adjusted so that the tip was just above the surface of the magnetically stirred solution in the distilling flask [KOH, 1.2 g.; 2-(2-ethoxyethoxy)ethanol, 7 ml.; tetrahydrofuran, 2 ml.; and H_2O, 2 ml.] heated in a water bath at 80–90°. Distillation of diazomethane was carried out *in situ* with the recommended safety measures.

Preparation of Salicylic Acid–Internal Standard and Aspirin–Internal Standard Calibration Curves—*Materials*—The following were used: (*a*) salicylic acid, Anachemia, reagent grade; (*b*) aspirin; USP reference standard; and (*c*) methyl *o*-methoxybenzoate (internal standard), Eastman, highest purity.

Solutions—The following were used: (*a*) diazomethane in tetrahydrofuran, prepared as described previously; (*b*) salicylic acid in tetrahydrofuran, accurately weighed to contain about 5 mg./ml.; and (*c*) internal standard in tetrahydrofuran, accurately weighed to contain about 5 mg./ml.

Preparation of Mixtures, Methylation, and GC—For the salicylic acid–internal standard calibration curve, the exact volume of solution required to give 5.00 mg. of internal standard was dispensed into each of eight separate flasks (5-ml. volumetrics are convenient) from a 5-ml. microburet (graduated in 0.01 ml.) with a 24-gauge 1.9-cm (0.75-in.) hypodermic needle delivery tip. The exact volumes of salicylic acid solution calculated to give weight ratios of salicylic acid–internal standard of 0.30, 0.70, 0.90, 1.10,

1.30, 1.70, 2.10, and 2.30 were then dispensed into respective flasks.

For the aspirin–internal standard calibration curve, samples containing approximately 50, 80, 100, 125, 150, and 170 mg. of aspirin, respectively, were accurately weighed into six separate small stoppered flasks. The exact volume of solution equivalent to 5.00 mg. of internal standard was then dispensed into each flask.

Each individual drug–internal standard solution was then treated as follows. No more than 15 min. prior to being chromatographed, the solution was treated with diazomethane (added dropwise with shaking) to a permanent yellow color, and then immediately placed in a frost-free freezer at −15° along with all solutions to be subsequently methylated. Within 10 min. after preparation, 1 μl. of the esterified solution was injected by means of a Hamilton microsyringe into a GC[1] equipped with a flame-ionization detector unit and fitted with a 5% OV-210 on Diatoport S (80/100 mesh) coiled glass column, 1.5-m. × 0.32-cm. (5-ft. × 0.13-in.) o.d. preconditioned at 265° for 18 hr. Salicylic acid and aspirin were isothermally eluted as their methyl esters under the following conditions: column temperature, 110°; injection port temperature, 180°; and detector temperature, 205°. Gas flows were: nitrogen, 28 ml./min.; and hydrogen, 28 ml./min. The detector signal was supplied to a continuous balance 1-mv. recorder[2], with a chart speed of 0.63 cm./min. (0.25 in./min), connected to a fully automatic printout electronic digital integrator[3] with an effective input signal range of 0–100 mv., thus permitting a constant attenuation setting of 1 × 4.

The area ratios of the methyl esters to internal standard were plotted against the weight ratios of salicylic acid or aspirin to internal standard, and the respective slopes of the lines of best fit were determined.

Preparation of Synthetic Aspirin–Salicylic Acid Mixtures, Tablet Sampling, and Analysis by GC—*Materials and Solutions*—The following were used: (*a*) aspirin, Merck, USP grade (salicylic acid content predetermined to be 0.12% by the USP procedure); (*b*) salicylic acid in tetrahydrofuran, accurately weighed to contain about 0.5 mg./ml. and 4 mg./ml.; and (*c*) internal standard in tetrahydrofuran, accurately weighed to contain about 5 mg./ml.

Preparation of Synthetic Mixtures—Into a flask (10-ml. volumetric is convenient), 75–150 mg. of aspirin was weighed accurately. Then the exact volume of solution equivalent to 5.00 mg. of internal standard was dispensed through a 5-ml. microburet. The appropriate volume of salicylic acid solution was then added to give the desired percentage of salicylic acid based on the total aspirin–salicylic acid weight.

Tablet Sampling—Ten tablets were selected at random, weighed, and finely powdered on a Micro-Mill[4] apparatus. A quantity of the powder equivalent to about 100 mg. of aspirin was accurately weighed out into a 10-ml. stoppered flask, and the exact volume of solution equivalent to 5.00 mg. of internal standard was added through the microburet.

Analysis—Each simulated mixture and powdered tablet sample was treated in turn with diazomethane and chromatographed as described previously. The amount of salicylic acid and aspirin in the synthetic mixture and powdered tablet aliquot was computed from the relationship $y = mx$, using m values of 0.971 and 1.069 for the aspirin–internal standard and salicylic acid–internal standard calibration curves, respectively, and y as the experimental peak area ratio of methyl ester to internal standard.

Analysis of Synthetic Aspirin–Salicylic Acid Mixtures and of Single-Component Aspirin Tablets by the USP Method—The simulated mixtures were prepared as described under *Preparation of Synthetic Mixtures*, except that the addition of internal standard was omitted. The solvent was removed by evaporation at room temperature, and the residue analyzed for salicylic acid content as stated in the USP monograph for aspirin tablets, with quantity modifications being made where necessary. The amount of aspirin was determined by spectrophotometric measurements at 280 nm. of the appropriately diluted initial chloroform eluate (which is discarded in the USP procedure) from the ferric chloride–urea column. No interference from any UV-absorbing species originating from the urea, ferric chloride, or siliceous earth was encountered.

[1] Varian Aerograph series 200, model 204-B.
[2] Minneapolis-Honeywell, Electronik 15 strip-chart recorder.
[3] Kent, model Chromalog 2.
[4] Chemical Rubber Co., Cleveland, Ohio.

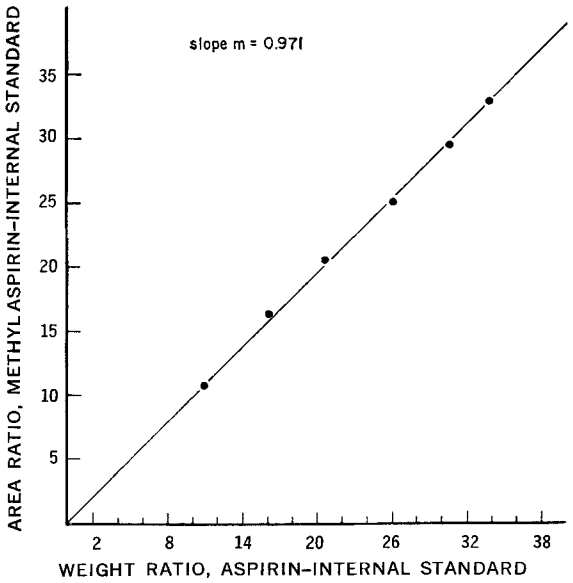

Figure 1—*Aspirin–internal standard calibration curve.*

The procedure followed for the single-component aspirin tablets was exactly as indicated in the monograph for aspirin tablets.

RESULTS

The area ratio *versus* weight ratio calibration curves for aspirin and salicylic acid are shown in Figs. 1 and 2, respectively. Both are straight lines passing through the origin ($y = mx$), and each point on the line represents the average of duplicate injections. With tetrahydrofuran as solvent, the precision between injections was excellent; the coefficient of variation computed from seven successive injections of a sample solution (kept at −15°) was ±0.35%. Detector response was linear for the weight ratio ranges investigated; salicylic acid was determined up to a ratio of 3.0:1 (not shown in the figure), and aspirin was determined up to a ratio of about 35:1. The mean slope for the aspirin line was 0.971, with a coefficient of variation of ±1.74%, while the values in the case of salicylic acid were 1.069 ± 1.12%. The calibration curves were checked about once a week over a 4-month period, but the drift from the lines was always less than their respective mean slope errors.

Because of the relatively large inaccuracies in weighing very small quantities of material (less than 10 mg.), a stock solution of salicylic acid in tetrahydrofuran was prepared and the calculated volume dispensed from a microburet into a flask containing an accurately weighed amount of aspirin. The theoretical percentages of salicylic

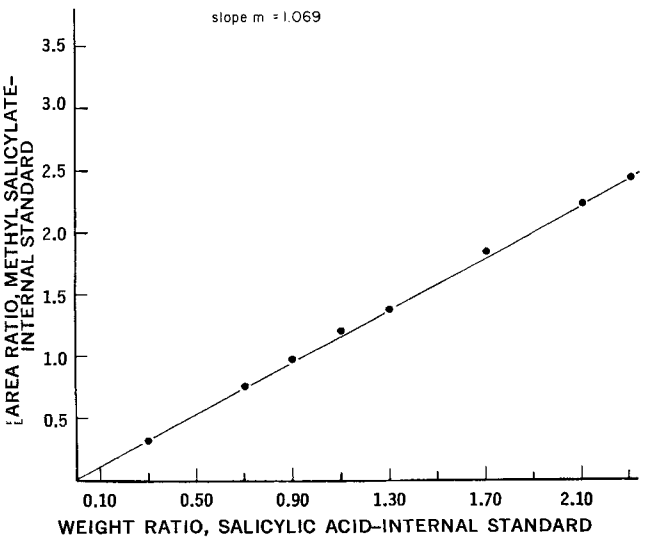

Figure 2—*Salicylic acid–internal standard calibration curve.*

Table I—Analysis of Aspirin–Salicylic Acid Synthetic Mixtures

Synthetic Mixture Number	Theoretical, %		Found—GC Method, %			Found—USP Method, %		
	Salicylic Acid	Aspirin	Salicylic Acid	Aspirin	Total Recovery	Salicylic Acid	Aspirin	Total Recovery
I	0.20	99.80	0.24	98.30	98.54	0.21	100.1	100.3
II	0.20	99.80	0.21	98.90	99.11	0.20	100.1	100.3
III	0.40	99.60	0.43	98.70	99.13	0.40	98.79	99.19
IV	0.40	99.60	0.40	98.81	99.21	0.39	99.35	99.74
V	0.60	99.40	0.57	100.0	100.6	0.56	98.57	99.13
VI	0.60	99.40	0.59	98.94	99.53	0.58	98.69	99.27
VII	0.80	99.20	0.75	98.97	99.72	0.76	98.71	99.47
VIII	0.80	99.20	0.77	98.75	99.52	0.77	98.92	99.69
IX	1.00	99.00	0.94	99.56	100.5	0.95	98.71	99.66
X	1.00	99.00	0.92	98.62	99.54	0.91	97.89	98.80
XI	3.00	97.00	2.99	96.51	99.50	2.89	95.86	98.75
XII	3.00	97.00	2.88	97.72	100.6	2.97	96.76	99.73
XIII	6.00	94.00	5.92	93.98	99.90	5.57	92.20	97.77
XIV	6.00	94.00	5.88	93.99	99.87	5.91	93.17	99.08
XV	10.00	90.00	10.14	89.66	99.80	9.83	89.25	99.08
XVI	10.00	90.00	10.21	89.96	100.2	9.78	90.71	100.5
					Mean 99.70% ±0.58%			Mean 99.40% ±0.68%

acid and aspirin in the synthetic mixtures were deduced on the basis of the total weight of drug. This type of sampling procedure was necessitated by the difficulty in achieving homogeneity of synthetic aspirin–salicylic acid mixtures made by addition of stock solution of both drugs followed by slow solvent evaporation; for all intents and purposes, samples analyzed by the GC and USP procedures were considered to be identical since they had been prepared in the same manner and from the same materials and solutions.

Inspection of Table I readily demonstrates the accuracy and precision obtainable with the GC procedure. The percentages of aspirin and salicylic acid found in the simulated mixtures were, without exception, very close to the theoretical values. The amount of drug found was calculated from the relationship $x = y/m$, where y is the experimental drug–internal standard area ratio, and m is the mean slope of the calibration curve. The average total drug recovery was 99.70%, with a standard deviation of ±0.58%. The mean total recovery with the USP procedure was 99.40 ± 0.68%.

In Table II, the results obtained when the GC technique was applied to the analysis of six brands of compressed and four brands of enteric coated single-component aspirin tablets are compared to those obtained with the USP procedure. In all cases, the agreement for aspirin percentage of label claim values was excellent. Product VII was the only sample found to be outside the USP limits for drug content and then only in a labeling sense, since it appears fairly evident from the data that it was formulated to contain 324 mg. aspirin per tablet. Nonaqueous titration of this sample against KOH in methanol with thymol blue as indicator gave an average percentage of label claim of 108.2%, further confirming the validity of the GC and USP results.

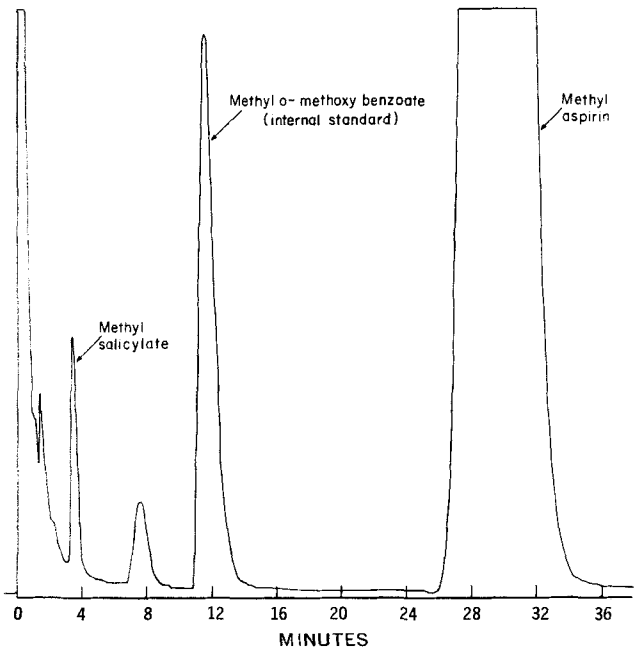

Figure 3—*GC of a methylated aspirin–salicylic acid mixture (salicylic acid ≃ 0.40%).*

The percentage of salicylic acid content determined by the two methods was found to be in line for most of the tablets examined; however, with Formulations I, VII, IX, and X, the amount of salicylic acid recovered was higher with the GC method than with the USP procedure. A problem that has been recognized as important in the determination of salicylic acid, particularly in buffered products, is the possibility of at least partial binding of the free acid by certain excipient materials to form chloroform-insoluble salts, resulting in underestimation of the true salicylic acid content. With this in mind, the USP assay for the mentioned samples was modified in turn to use different extraction media: (*a*) prior trituration of the powder with 1 ml. tetrahydrofuran, (*b*) the extraction medium of Guttman and Salomon (13) (citric acid and chloroform), and (*c*) that suggested by Shane and Miele (7) (HCl–citric acid and chloroform). None of these media, however, effected any increase in the salicylic acid recovery by the USP method, nor did injection of the methylated mixture at various time intervals give any change by the GC procedure.

DISCUSSION

Preparation of Diazomethane and Reaction with Aspirin and Salicylic Acid—Of the methods encountered in the literature for the preparation of diazomethane, the procedure described by Deboer and Backer (12) was considered to be the least hazardous from the point of view of toxicity of starting materials and of relative safety from explosion. All recommended precautionary measures were observed and the reaction quantities were scaled down 10-fold using tetrahydrofuran as the solvent. The yield of diazomethane thus obtained was conveniently sufficient for the methylation of several samples (usually about 10). The choice of solvent was dictated by several factors.

1. The much greater solubility of aspirin in tetrahydrofuran precluded the possibility of loss by fractional crystallization (thereby changing the aspirin–salicylic acid weight ratio) and thereby allowing a higher degree of precision than is possible with the more volatile diethyl ether.

2. The considerably smaller flame-ionization detector (FID) response to the former solvent gave better resolution and concomitant greater reliability of the methyl salicylate peak area integration.

3. A greater yield of diazomethane was obtained with tetrahydrofuran despite a generally longer reaction time.

The ease of hydrolysis of aspirin to salicylic acid when subjected to even trace amounts of hydroxyl ion necessitated distillation of

Table II—Analysis of Single-Component Aspirin Tablets

Product Number	Type	Label Dosage Level, mg./tablet	Found—GC Method, % Label Claim		Found—USP Method, % Label Claim	
			Salicylic Acid	Aspirin	Salicylic Acid	Aspirin
I	Compressed	453.6	0.11	100.8	0.05	98.40
			0.11	99.56	0.05	100.0
II	Compressed	324.0	0.14	100.7	0.13	100.1
			0.14	100.5	0.13	99.38
III	Compressed	324.0	0.07	99.91	0.05	100.0
			0.08	98.37	0.05	100.1
IV	Enteric coated	324.0	0.39	97.93	0.35	101.4
			0.42	98.76	0.38	100.4
V	Enteric coated	324.0	0.22	94.96	0.17	95.63
			0.22	96.71	0.18	95.95
VI	Compressed	324.0	0.12	98.42	0.08	100.6
			0.15	99.71	0.08	100.2
VII	Compressed	300.0	0.19	108.4	0.10	110.1
			0.21	107.4	0.11	110.1
VIII	Enteric coated	600.0	0.93	103.1	0.91	103.0
			0.90	101.5	0.96	102.9
IX	Enteric coated	324.0	4.59	92.37	3.07	93.97
			4.52	95.18	3.13	95.03
X	Compressed	81.0	0.20	101.2	0.12	102.6
			0.21	101.2	0.11	103.6

the product from the strongly alkaline reaction mixture. The yellow distillate was stable over a period of about a week when kept tightly stoppered under refrigeration at −15°.

In a study of phenolic aromatic acids, Seoane and Carnicer (14) concluded, on the basis of pKa considerations, that diazomethane should react completely with salicylic acid without forming any dimethylated compound, but they did not discuss the somewhat analogous case of aspirin in the presence of excess diazomethane. In the present work, when aspirin solutions were treated with diazomethane and stored at room temperature for 3 hr. or more, the conversion of aspirin to methylaspirin was attended by the slow formation of an artifact having retention time closely similar to that of methyl *o*-methoxybenzoate. Whatever the nature of this reaction, it was completely prevented by cooling the methylated sample solution in a frost-free freezer at −15° immediately after preparation and between successive injections of the same sample solution.

As an added measure to preclude artifact formation, thereby ensuring the correctness of the internal standard (methyl *o*-methoxybenzoate) peak area integration, addition of diazomethane to each sample solution was carried out no more than 15 min. prior to chromatography. The esterification was rapid and complete within 5 min. at −15°, and it was without vigorous effervescence when tetrahydrofuran was employed as the solvent. Preparation of the trimethylsilyl derivatives with the BSA[5] reagent was also attempted, but the results appeared to be less satisfactory. The observation of Rowland and Riegelman (10) on the appearance of two derivative peaks for salicylic acid was confirmed but was not investigated further.

GC of the Methyl Esters—GC of aspirin and salicylic acid as the free acids is often accompanied by considerable tailing of the peaks, due mainly to binding of the hydroxyl groups with active adsorption sites on the solid support. It is, therefore, usually necessary to convert these drugs to less polar derivatives (15) and to select a liquid stationary phase which will be relatively nonretentive in order to achieve optimum separation with a minimum of tailing. This is especially important if the peak areas are to be measured accurately. OV-210 is particularly suitable in this respect; under normal conditions of usage, a column of this type exhibits little or no bleedoff.

Figure 3 shows the clearcut separation of the peaks of interest at the low column temperature used in this work. The injection port temperature was kept at an optimum 180°; higher temperatures were found to induce some hydrolysis of the methylaspirin, giving spurious results. The extraneous peak at around 8 min. was due to the stabilizing agent, butylated hydroxyanisole, added to tetrahydrofuran to prevent excessive peroxide formation on storage. However, it was well resolved from the highly symmetrical methyl salicylate, internal standard, and methylaspirin peaks and did not affect the accuracy of the results. Operating isothermally, the total running time for a complete aspirin–salicylic acid analysis was 35 min., only 15 min. being required for the determination of salicylic acid.

Methyl *o*-methoxybenzoate fulfilled all of the criteria of a suitable internal standard; it was well resolved from and eluted close to the other peaks of interest and is of closely similar molecular structure to the compounds being measured. Indeed, area ratio *versus* weight ratio data interpolated from the calibration curves (Figs. 1 and 2) implied, as expected, an almost identical FID response to methyl salicylate, methylaspirin, and methyl *o*-methoxybenzoate. The low levels of salicylic acid usually found in aspirin raw material and commercial dosage forms will generally require a low attenuation setting and a methylaspirin solution of sufficiently high concentration (20–30 mg./ml.) in order to obtain a methyl salicylate peak of area amenable to accurate quantitation. As a result, the methylaspirin peak will invariably be off-scale so that its accurate measurement can be most conveniently achieved with an electronic digital integrator capable of accepting a wide range of input signals (up to 100 mv.). In practice, the signal level output from the detector on methylaspirin elution was in the range of 15–30 mv., which permitted a constant attenuation setting and a minimum of dial switching.

CONCLUSION

The present official procedures for the analysis of salicylic acid and aspirin are tedious and time consuming and require the expertise of a skilled analyst to obtain optimum accuracy and precision. They may be satisfactory for small numbers of individual samples but are not entirely feasible for large-scale investigational or quality control work which demands a relatively high data output. The GC method described here for the simultaneous analysis of aspirin and salicylic acid in synthetic mixtures is rapid, accurate, and precise and would appear to be more suitable for the types of surveys mentioned. A subsequent paper will deal with the analysis of multicomponent aspirin tablets by the proposed technique.

REFERENCES

(1) "United States Pharmacopeia," 17th rev., Mack Publishing Co., Easton, Pa., 1965, p. 50.

(2) J. D. Weber and J. Levine, *J. Pharm. Sci.*, **55**, 78(1966).

(3) J. Levine and J. D. Weber, *ibid.*, **57**, 631(1968).

(4) "British Pharmacopoeia," General Medical Council, The Pharmaceutical Press, London, England, 1968, p. 65.

(5) Song-Ling Lin, *J. Pharm. Sci.*, **56**, 1130(1967).

(6) K. H. Lee, L. Thompkins, and M. R. Spencer, *ibid.*, **57**, 1240(1968).

(7) N. Shane and D. Miele, *ibid.*, **59**, 397(1970).

[5] Pierce Chemical Co.

(8) C. I. Miles and G. H. Schenk, *Anal. Chem.*, **42**, 656(1970).
(9) J. G. Nikelly, *ibid.*, **36**, 2248(1964).
(10) M. Rowland and S. Riegelman, *J. Pharm. Sci.*, **56**, 717(1967).
(11) R. C. Crippen and H. C. Freimuth, *Anal. Chem.*, **36**, 273(1964).
(12) T. J. Deboer and H. J. Backer, *Org. Syn.*, **36**, 16(1956).
(13) D. E. Guttman and G. W. Salomon, *J. Pharm. Sci.*, **58**, 120(1969).
(14) E. Seoane and A. Carnicer, *Microchem. J.*, **12**, 291(1967).
(15) C. H. Morris, J. E. Christian, R. R. Landolt, and W. G. Hansen, *J. Pharm. Sci.*, **59**, 270(1970).

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Analysis of Barium in Barium Sulfate and Diagnostic Meals Containing Barium Sulfate Using Atomic Absorption Spectroscopy

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Abstract □ An analytical method was developed for the determination of barium in barium sulfate and diagnostic meals containing barium sulfate using atomic absorption spectroscopy. The procedure provides satisfactory levels of accuracy and precision and overcomes many disadvantages of currently used procedures such as lack of barium specificity, lengthy analysis time, and interference by diagnostic meal additives.

Keyphrases □ Barium—determination □ Diagnostic meals, barium sulfate—barium determination □ Atomic absorption spectroscopy—analysis

Barium sulfate has been the medium of choice for roentgenographic examination of the gastrointestinal tract for over half a century. In spite of its long use, an assay procedure was not included in the USP until publication of the 18th revision. Major drawbacks that contribute singly or collectively to the shortcomings of existing methods of barium sulfate analysis include lack of accuracy, lack of precision, excessive cost, and lengthy analysis time.

Several analytical techniques have been developed for barium analysis. These include: complexometric procedures using ethylenediaminetetraacetic acid (EDTA) as the titrant (1, 2), flame emission spectroscopy (3), X-ray (4), anodic arc excitation spectrography (5), gravimetry (6–8), and turbidimetry (9, 10). A gravimetric method based on fusion of the sample with sodium carbonate followed by precipitation of barium as barium chromate is the official assay procedure found in USP XVIII (11).

The introduction of atomic absorption spectroscopy (AAS) as a new analytical tool offers another approach for the assay of barium sulfate. The method is very sensitive and highly specific for barium ion (12). Roe *et al.* (13) reported a method for the estimation of low concentrations of sulfur and sulfate in biological materials by conversion of sulfate to barium sulfate and subsequent barium determination by AAS. The objective of this investigation is to evaluate atomic absorption spectroscopy as a method for barium content determination of barium sulfate and diagnostic meals containing barium sulfate.

EXPERIMENTAL

Equipment—A Perkin-Elmer model 290 atomic absorption spectrophotometer with a single slot, model 290-1169, burner head and a Perkin-Elmer Intensitron barium lamp were used for barium content determinations. A lamp current of 7 mamp. was used. The instrument slit width was set at 7 Å, and a meter damper setting of 3 was used. The instrument was adjusted to a coarse select element setting of approximately 709.7. Standard tanks of compressed air and acetylene were used with regulator settings of 40 and 8 psig., respectively. The instrument fuel flow was adjusted to approximately 14.1 and the air flow to approximately 14.8.

Reagents—The initial consideration in the development of an AAS method of analysis for barium sulfate was to find a solvent system in which barium sulfate would be readily soluble. This chemical is virtually insoluble in water and other solvents suitable for use in AAS (14, 15). Organic solvents, such as dimethyl sulfoxide and *N,N*-dimethylformamide, and aqueous solutions containing selected inorganic salts, such as zirconium nitrate and zirconium chloride, were evaluated experimentally and found to be unsuitable as solvent systems. In the course of the solubility study, ethylenediaminetetraacetic acid and its salts were also investigated. It was found that a 0.05 *M* disodium ethylenediaminetetraacetic acid (Na_2EDTA) solution USP XVIII, adjusted to pH 10 with 2 *N* sodium hydroxide solution had solubility properties suitable for the analytical procedure.

Because USP reference standard barium sulfate was not available for the preparation of a barium standard curve, barium sulfate USP was purified in the following manner. The material was dissolved in concentrated sulfuric acid, precipitated by dilution with distilled water, collected by vacuum filtration through a fritted-glass filter, dried, and finally ignited at 1000° for 4 hr. The process was repeated twice, and the purified barium sulfate was stored over silica gel. The barium chloride evaluated for standard curve samples was reagent grade containing 2 moles of water of crystallization. Lanthanum chloride was obtained from a commercial supply house and was of unknown grade. Barium sulfate USP and two commercial diagnostic meals containing barium sulfate were used in the evaluation study. The barium sulfate was obtained from a single lot and assayed following the USP XVIII gravimetric procedure with one exception. The barium sulfate and sodium carbonate mixture was fused using a muffle furnace instead of a blast burner. After the clear melt was obtained, it was then heated at 1000° for 30 min. The results of three determinations were 98.95, 99.92, and 100.0%. The two commercial sources of diagnostic meal were also obtained from single lots.