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Simultaneous GLC Analysis of Aspirin and Nonaspirin Salicylates in Pharmaceutical Tablet Formulations

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Abstract □ The analysis of aspirin and nonaspirin salicylates in buffered and plain tablet formulations employing nearly nonaqueous extraction is described. The results obtained compare favorably with those obtained from USP procedures. A simultaneous assay for aspirin and nonaspirin salicylates in buffered tablets involves the use of an acidified chromatographic siliceous earth column for the separation of the aspirin and nonaspirin salicylates from various buffers or antacids. The column is eluted with chloroform, and the aspirin and nonaspirin salicylates are analyzed by GLC as their trimethylsilyl derivatives. The methods described here have definite advantages over USP XX procedures, and the buffered aspirin tablet procedure also is adaptable to aspirin formulations containing codeine, acetaminophen, propoxyphene, caffeine, and many antihistamines.

Keyphrases □ Aspirin—simultaneous GLC analysis with nonaspirin salicylates in tablet formulations □ Salicylates, nonaspirin—simultaneous GLC analysis with aspirin in tablet formulations □ GLC—analysis, aspirin and nonaspirin salicylates in tablet formulations

The GLC analysis of aspirin and nonaspirin salicylates in solid pharmaceutical dosage forms and biological fluids has been reported (1–18). The extraction of nonaspirin salicylates from various buffers is accomplished by the current USP procedure; however, the USP procedure for the analysis of aspirin does not effectively free aspirin from aged tablets containing calcium, aluminum, and magnesium buffers. Complexation of aspirin and nonaspirin salicylates with buffers has been reported (19–22). The current USP spectrophotometric procedures for aspirin tablets may not separate impurities such as acetylsalicylsalicylic acid and acetylsalicylic acid anhydride (23–27). Analysis of aspirin and nonaspirin salicylates by high-pressure liquid chromatography (HPLC) also has been reported (28–35). Mobile phases and extractions employing methanol and water, even in small quantities, result in unavoidable hydrolysis of aspirin, thereby giving variable and nonreproducible quantitation of salicylic acid.

The buffered aspirin tablet procedure described here enables the extraction of both aspirin and nonaspirin salicylates from excipients and buffers in a virtually nonaqueous procedure, thereby keeping hydrolysis of aspirin to a minimum.

EXPERIMENTAL

Materials—Aspirin USP reference standard (GLC purity 99.95%), salicylic acid USP reference standard (GLC purity 100.0%), chromatographic siliceous earth prepared by the USP procedure, propylparaben USP, and *N,O*-bis(trimethylsilyl)acetamide were used. Chloroform and hydrochloric acid were reagent grade.

Simultaneous GLC Analysis of Aspirin and Nonaspirin Salicylates in Buffered Tablets—*Internal Standard Solution*—About 425 mg of propylparaben USP was diluted to 100 ml with chloroform and mixed.

Aspirin Standard Preparation—About 125 mg of aspirin USP reference standard was weighed accurately, transferred to a 50-ml volumetric flask, diluted to volume with chloroform, and mixed. The standard preparation was derivatized within 2 hr of preparation.

Salicylic Acid Standard Preparation—About 15 mg of salicylic acid USP reference standard was weighed accurately, transferred to a 200-ml volumetric flask, diluted to volume with chloroform, and mixed.

Assay Preparation—The average tablet weight of 20 tablets was determined, and the tablets were ground to a fine powder. Without delay, a portion of the ground tablets equivalent to 500 mg of aspirin was transferred to a small beaker containing 3.0 g of acid-washed chromatographic siliceous earth. The powders were mixed with a glass rod, 2.0 ml of 6 *N* HCl was added, and the powders were mixed again with the glass rod. The mixture was transferred to a 20 × 2.5-cm chromatographic column, and the beaker was dry washed with 1.0 g of siliceous earth (glass wool was used at both ends of the column).

The column was packed uniformly and eluted with successive portions of chloroform *via* the sample beaker at the rate of ~10 ml/min. About 150 ml of the eluate was collected in a 200-ml volumetric flask. The tip

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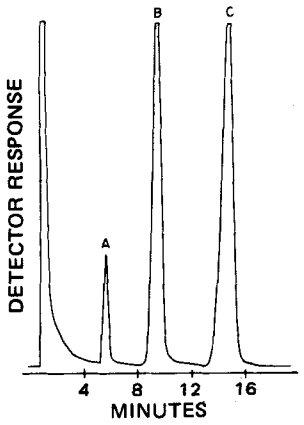

Figure 1—*Gas chromatogram of the trimethylsilyl derivatives of salicylic acid (a), aspirin (b), and the internal standard, propylparaben (c), for buffered aspirin tablets.*

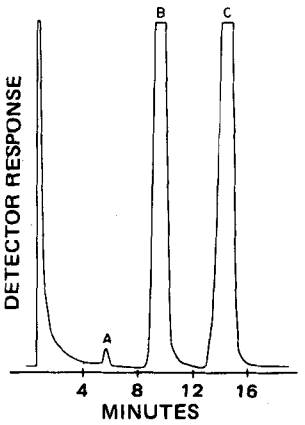

Figure 2—*Gas chromatogram of the trimethylsilyl derivatives of salicylic acid (a), aspirin (b), and the internal standard, propylparaben (c), for aspirin tablets.*

of the column was rinsed with chloroform, and the flask was brought to volume and mixed. The chloroform elution was conducted within 30 min of column packing, and the powdered tablets were sampled within 1 hr of grinding.

Procedure—Aliquots (2.0 ml) of the aspirin standard preparation, the salicylic acid standard preparation, and the assay preparation were transferred to separate reaction vials. A 1.0-ml aliquot of the internal standard solution was added to each vial. The contents of all of the vials were derivatized using 250 μl of *N,O*-bis(trimethylsilyl)acetamide with vigorous mixing for 30 sec.

All vials were vented and heated at 60° for ~15 min and then cooled to room temperature for subsequent injection into the gas chromatograph. (The derivatized solutions are stable for 4 days in airtight containers.) The gas chromatograph[1] was equipped with a flame-ionization detector and an electronic integrator[2]. The glass column typically was 180 cm × 2 mm and was packed with 3% phenyl methyl silicone liquid phase (OV-17) on 100–120-mesh chromatographic silanized siliceous earth[3].

The temperatures of the injection port, column, and detector were 180, 120, and 140°, respectively. The carrier gas was nitrogen at a flow rate of ~35 ml/min. Relative retention times for the trimethylsilyl derivatives of salicylic acid, aspirin, and propylparaben were 0.36, 0.63, and 1.0, respectively (Fig. 1). In a suitable chromatogram, the resolution factor was not <2.0 between any two peaks, and the relative standard deviation was not >2.0 for five replicate injections of the standard preparation. At the completion of each sample chromatogram, the column temperature was raised to 240° for 3 min to purge the column of tablet excipients.

Calculations—The quantities (in milligrams) of aspirin and salicylic acid in the portion taken for the assay preparation were calculated by the same formula, $100C(R_u/R_s)$, in which C is the concentration (in milligrams per 2.0 ml) of the appropriate USP reference standard in the standard preparation and R_u and R_s are the ratios of the peak areas of the corresponding analyte to those of the internal standard obtained with the assay preparation and the standard preparation, respectively.

Simultaneous GLC Analysis of Aspirin and Nonaspirin Salicylates in Aspirin Tablets—*Internal Standard Solution*—About 1.7 g of propylparaben USP was diluted to 100 ml with chloroform and mixed.

Aspirin Standard Preparation—About 100 mg of aspirin USP reference standard was weighed accurately and transferred to a 50-ml glass-stoppered flask.

Salicylic Acid Standard Preparation—About 30 mg of salicylic acid USP reference standard was weighed accurately, transferred to a 100-ml volumetric flask, diluted to volume with chloroform, and mixed. A 1.0-ml aliquot was transferred to a 50-ml glass-stoppered flask.

Assay Preparation—The average tablet weight of 20 tablets was determined, and the tablets were ground to a fine powder. A portion of the ground tablets equivalent to 100 mg of aspirin was transferred to a 50-ml glass-stoppered flask.

Procedure—A 5.0-ml aliquot of the internal standard solution and 15 ml of chloroform were transferred to each 50-ml glass-stoppered flask containing the standards and assay preparations. All solutions were shaken mechanically for exactly 3 min and filtered. Without delay, a 2.0-ml portion of each solution was derivatized with 300 μl of *N,O*-bis(trimethylsilyl)acetamide, shaken for 30 sec, and heated at 60° for ~15 min. The GLC analysis (Fig. 2) was conducted as described for the buffered aspirin tablets.

Calculations—The quantity (in milligrams) of aspirin in the portion taken for the assay preparation was calculated from $C(R_u/R_s)$, in which C is the concentration (in milligrams) of the USP reference standard in the standard preparation and R_u and R_s are the ratios of the peak areas of the corresponding analyte to those of the internal standard obtained with the assay preparation and the standard preparation, respectively. The nonaspirin salicylates were determined on a pass or fail 0.3% limit standard.

RESULTS AND DISCUSSION

Linearity and Precision—The response linearity for the described GLC methods was suitable for the entire assay range. The precision on multiple injections into the chromatograph was ±0.45% for the aspirin analysis and ±1.0% for the nonaspirin salicylate analysis.

Assay Specificity—Recoveries of aspirin and salicylic acid mixtures from the chromatographic siliceous earth column averaged 99.9 and 99.8%, respectively. None of the commercial products analyzed produced any GLC interference. A comparison of the GLC analysis to the USP procedure for buffered aspirin tablets and plain aspirin tablets is shown in Tables I and II, respectively. Table III shows the results of the GLC analysis of aspirin tablets containing aluminum and magnesium hydroxides.

Because of the good response linearity of the salicylic acid trimethylsilyl derivative, the actual percentages were calculated from a single-point

Table I—Assay Results on Commercial Buffered Aspirin Tablets

Product	Aspirin, % of claim		Nonaspirin Salicylates, %	
	GLC Method	USP Method	GLC Method	USP Method
A	98.3	96.5	0.68	0.58
B	98.2	98.2	0.73	0.75
C	97.8	98.1	0.60	0.57
D	93.1	94.5	0.41	0.36
E	95.7	93.5	1.55	1.48
SD[a]	1.51		0.045	

[a] Standard deviation of the GLC method compared to the USP method.

Table II—Commercial Aspirin Tablets

Product	Aspirin, % of claim		Nonaspirin Salicylates, %	
	GLC Method	USP Method	GLC Method	USP Method
F	100.2	99.3	<0.3	<0.3
G	100.5	100.9	<0.3	<0.3
H	99.4	96.9	<0.3	<0.3
I	102.0	99.8	<0.3	<0.3
J	99.5	98.4	<0.3	<0.3
SD[a]	1.15			

[a] Standard deviation of the GLC method compared to the USP method.

[1] Hewlett-Packard model 7620A.
[2] Hewlett-Packard model 3370A.
[3] Applied Science Laboratories, State College, Pa.

Table III—GLC Assay Results on Aspirin Tablets Containing Magnesium and Aluminum Hydroxides

Lot	Age	Aspirin, % of claim	Nonaspirin Salicylates, %
1	1 week	98.4	0.18
2	2 weeks	99.4	0.23
3	2 weeks	98.3	0.25
4	2 weeks	99.1	0.28
5	3 weeks	97.5	0.33
6	3 weeks	98.5	0.26
7	4 weeks	101.6	0.28
8	5 weeks	100.5	0.45
9	6 weeks	100.6	0.47
10	6 weeks	100.9	0.26
11	3 years	98.5	0.89
12	3 years	96.3	0.95
13	3 years	98.0	0.80
14	4 years	99.2	0.77
15	4 years	98.2	0.99
16	4 years	98.4	0.82
SD[a]		1.21	0.032

[a] Average standard deviation of duplicate analyses.

standard in the analysis of buffered tablets. The average aspirin assay for 21 determinations of buffered tablets by the GLC and USP procedures was 98.4 and 98.7%, respectively. The same values for 21 analyses of the nonaspirin salicylates were 0.58 and 0.58%, respectively. Plain aspirin tablets were determined on a pass or fail 0.3% limit standard. Analysis of aspirin in combination with codeine, caffeine, acetaminophen, propoxyphene, and many antihistamines, although not reported here, gave good results by a modified GLC procedure as described for buffered aspirin tablets.

Hydrolysis of Aspirin—Chromatographic siliceous earth has been used extensively as a partitioning medium for aspirin analysis (36–42). The USP employs this material with a ferric chloride–urea reagent to complex salicylic acid. The use of siliceous earth in the procedure described here is not as a partitioning medium but rather as a distribution and absorption medium. In this study, 2.0 ml of 6 *N* HCl was used for all commercial tablets tested. In practice, the acid strength can be adjusted so that it is in slight excess of the amount needed to neutralize the buffers in the tablet.

The siliceous earth incorporated with the 6 *N* HCl and the ground tablet distributes the drug over a large surface area and adsorbs the buffers on the acidified surface, releasing the aspirin and nonaspirin salicylates to the chloroform eluent. The 2.0 ml of 6 *N* HCl is retained on the siliceous earth surface and has the capacity to solubilize ~7 mg of the 500 mg of aspirin sample taken for assay. However, the buffers and tablet excipients, together with the siliceous earth, adsorb the available acid, thereby minimizing hydrolysis. The extraction is virtually nonaqueous, and the aspirin is out of solution.

A previous report described the hydrolysis and kinetics of aspirin in relation to solution and concentration, giving a much lower hydrolysis rate of the drug out of solution (43). The hydrolysis rate of aspirin induced by the siliceous earth column was determined to be ~0.06% for 30 min. In practice, the chloroform elution was conducted within 15 min of column packing. Texts (44, 45) and review articles (46, 47) have detailed the decomposition, hydrolysis, and kinetics of aspirin with a list of over 300 references.

CONCLUSIONS

Multiple analyses of aspirin and nonaspirin salicylates in solid pharmaceutical dosage forms have been difficult and time consuming by the USP procedures. The USP procedure is stability indicating for nonaspirin salicylates but not for aspirin. The GLC procedures described here are less time consuming and lend themselves to multiple analysis on a gas chromatograph equipped with an automatic injector. In practice, a chemist can prepare 15–20 samples daily employing the buffered aspirin tablet procedure and up to 40 samples daily with the plain aspirin tablet procedure. Beside the savings in analytical costs, these procedures are stability indicating and adaptable to many pharmaceutical solid dosage forms of aspirin.

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