Hz, CH_2CH_3), 2.74 [m, 6, $N(CH_2)_3$], 3.9 (s, 2, OCH_2), 7.06, 7.18 (doublets, J = 3.5 Hz, 2, 3,4-furan CH), 7.61, 7.89 (doublets, J = 9.0 Hz, 4, phenyl CH), and 10.8 (b, 1, HCl)

Other I esters had similar NMR spectra except for expected variations due to various phenyl substitutents. Other pertinent data are summarized in Table I.

The I esters were evaluated initially *in vitro* on the rabbit ileum as described previously (7). Each drug was dissolved in distilled water for administration.

REFERENCES

(1) H. R. Snyder, Jr., C. S. Davis, R. K. Bickerton, and R. P. Halliday, *J. Med. Chem.*, **10**, 807 (1967).

(2) T. J. Schwan and K. O. Ellis, *J. Pharm. Sci.*, **64**, 1047 (1975).

(3) R. L. White and T. J. Schwan, *ibid.*, **65**, 135 (1976).

(4) G. C. Wright, H. A. Burch, and M. M. Goldenberg, U.S. pat. 3,856,825 (Dec. 1974).

(5) C. M. Suter, "Medicinal Chemistry," vol. I, Wiley, New York, N.Y., pp. 151–220.

(6) C. S. Davis and G. S. Lougheed, *J. Heterocycl. Chem.*, **4**, 153 (1967).

(7) M. M. Goldenberg, *Arzneim.-Forsch.*, **26**, 341 (1976).

(8) M. M. Goldenberg, *Arch. Int. Pharmacodyn. Ther.*, **222**, 27 (1976).

(9) H. Akashi and R. Oda, *J. Chem. Soc. Jpn., Ind. Sect.*, **55**, 271 (1952); through *Chem. Abstr.*, **48**, 3953f (1954).

(10) *Ibid.*, **53**, 202 (1950); through *Chem. Abstr.*, **46**, 9312i (1952).

(11) K. Hayes and G. Drake, *J. Org. Chem.*, **15**, 873 (1950).

ACKNOWLEDGMENTS

F. Abbott, R. Burns, J. Clark, J. Curtis, P. Curtis, R. Finch, D. George, G. Gustin, C. Jeffrey, G. Lougheed, N. Miles, W. Smith, B. Stevenson, M. Tefft, and A. Winterstein are acknowledged for their technical assistance in the preparation, analysis, and biological evaluation of the compounds.

Simultaneous Quantitation of Acetaminophen, Aspirin, Caffeine, Codeine Phosphate, Phenacetin, and Salicylamide by High-Pressure Liquid Chromatography

V. DAS GUPTA

Received May 7, 1979, from the *Department of Pharmaceutics, College of Pharmacy, University of Houston, Houston, TX 77004.* Accepted for publication July 31, 1979.

Abstract □ A method for the simultaneous quantitation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide was developed. The method is based on reversed-phase high-pressure liquid chromatography with a mobile phase buffered with phosphate (pH 2.3). The procedure not only separated these six active ingredients but also salicylic acid, the major decomposition product of aspirin. The method gave excellent results for three commercial products and a synthetic mixture containing four active ingredients. Lowering the pH increased the retention time of some weak acids and decreased that of some weak bases. Only these changes in the retention times made the separation possible.

Keyphrases □ High-pressure liquid chromatography—simultaneous quantitation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide □ Acetaminophen—simultaneous quantitation with aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide, high-pressure liquid chromatography □ Aspirin—simultaneous quantitation with acetaminophen, caffeine, codeine phosphate, phenacetin, and salicylamide, high-pressure liquid chromatography □ Caffeine—simultaneous quantitation with acetaminophen, aspirin, codeine phosphate, phenacetin, and salicylamide, high-pressure liquid chromatography □ Codeine phosphate—simultaneous quantitation with acetaminophen, aspirin, caffeine, phenacetin, and salicylamide, high-pressure liquid chromatography □ Phenacetin—simultaneous quantitation with acetaminophen, aspirin, caffeine, codeine phosphate, and salicylamide, high-pressure liquid chromatography □ Salicylamide—simultaneous quantitation with acetaminophen, aspirin, caffeine, codeine phosphate, and phenacetin, high-pressure liquid chromatography

About 80 commercially available nonprescription drugs (1) contain one or more pain relievers such as acetaminophen, aspirin, phenacetin, and salicylamide. Many of them also contain caffeine and buffering agents such as aluminum hydroxide and magnesium hydroxide (1). At least two commercial products contain a combination of acetaminophen, aspirin, caffeine, and salicylamide (1). Other products contain a combination of acetaminophen or aspirin, caffeine, phenacetin, and salicylamide (1). Many prescription drugs contain codeine phosphate, usually combined with aspirin, caffeine, and phenacetin.

BACKGROUND

The simultaneous quantitation of these ingredients is difficult. The NF methods (2) for the quantitation of aspirin, caffeine, codeine phosphate, and phenacetin in combination are tedious and time consuming. The colorimetric (3) and fluorometric (4) methods for aspirin quantitation are based on its hydrolysis to salicylic acid. Since salicylic acid is the principal decomposition product of aspirin, these methods are not specific. The GLC method (5) for aspirin quantitation is more specific but requires derivatization, which takes ~1 hr and can be complicated by the hydrolysis of aspirin to salicylic acid.

Previous investigators (6) reported that aspirin-containing combinations were difficult to chromatograph using nonpolar solvents and normal-phase chromatography. They preferred (7) paired-ion chromatography using the tetrabutylammonium ion to separate aspirin from muscle relaxants. They did not apply this method to separate combinations of the various pain relievers mentioned.

An automated high-pressure liquid chromatographic (HPLC) method (8) for the quantitation of aspirin, caffeine, and phenacetin was reported. The investigators used a controlled pore glass support as the stationary column and 8% acetic acid in chloroform as the mobile phase. This method was not tried on other pain relievers or in the presence of codeine phosphate.

Another HPLC method (9) analyzed small aspirin quantities in plasma in the presence of large salicylic acid quantities. However, the salicylic acid quantity is very small and the aspirin quantity is high in the dosage forms.

One study (10) used macroporous poly(methyl methylacrylate) resin to assay aspirin. This method was tedious and complicated. Two columns and two solvents were used to analyze some pain reliever combinations.

The purposes of the present investigations were to: (*a*) develop a rapid

0022-3549/80/0100-0108$01.00/0

Table I—Assay Results [a] of Commercial Dosage Forms and Synthetic Mixture

Ingredient	Commercial Sample 1		Commercial Sample 2		Commercial Sample 3		Synthetic Mixture	
	Claim per Tablet, mg	Found, % claim	Claim per Tablet, mg	Found, % claim	Claim per Tablet, mg	Found, % claim	Added, g	Found, % claim
Acetaminophen (I)	97.2	98.6	—	—	325	99.0	1.00	99.4
Aspirin (II)	194.4	99.6	226.8	99.6	—	—	1.00	99.1
Salicylamide (III)	129.6	100.0	—	—	—	—	1.00	99.9
Caffeine (V)	64.8	99.1	32.4	100.9	—	—	0.30	100.7
Codeine phosphate (VI)	—	—	—	—	30	99.1[b]	—	—
Phenacetin (VII)	—	—	162.0	99.2[c]	—	—	0.30	100.5

[a] The relative percent standard deviations based on five repeated injections were: 1.8, 1.6, 1.5, 1.3, 1.2, and 1.5 for I, II, III, V, VI, and VII, respectively. [b] Assayed at 285 nm for better sensitivity. [c] Assayed at a sensitivity of 0.1 instead of further dilution and reinjection.

and simple HPLC method for the simultaneous quantitation of six active ingredients (acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide), and (*b*) develop a method free of interference from salicylic acid, the principal aspirin decomposition product.

EXPERIMENTAL

Reagents and Chemicals—All reagents and chemicals were ACS, USP, or NF quality and were used without further purification.

Apparatus—The high-pressure liquid chromatograph[1] was connected to a multiple-wavelength[2] detector, a recorder[3], and an integrator[4].

Column—The nonpolar column[5] (30 cm × 4 mm i.d.) consisted of a monomolecular layer of octadecyltrichlorosilane permanently bonded by silicone–carbon bonds.

Chromatographic Conditions—Solvent A consisted of 0.01 *M* KH_2PO_4 in water with 19% (v/v) methanol (±1%) whose pH[6] was adjusted to 2.3 with an 85% aqueous phosphoric acid solution (~1.1 ml/liter was required). Any methanol concentration between 18 and 20% could be used, but the retention times differed slightly. The exact concentrations used were reported with the sample chromatograms. Solvent B was the same as Solvent A, except that no phosphoric acid was added and the pH was ~4.85.

The temperature was ambient. The flow rate was 2.0 ml/min. The detector sensitivity was 0.04 (254 nm), except for acetaminophen peaks where it was 0.2. For the phenacetin analysis, the sensitivity was 0.1. For codeine analysis, 285 nm was preferred due to greater sensitivity. The chart speed was 30.5 cm/hr.

Solution Preparation—The stock solutions of acetaminophen (I), aspirin (II), salicylamide (III), and salicylic acid (IV) were prepared by dissolving 0.100 g in 5 ml of ethanol and bringing the solution to 100.0 ml with water. Aspirin solutions always were prepared immediately before use. Similar stock solutions of caffeine (V) and codeine phosphate (VI) were prepared without ethanol. The stock solution of phenacetin (VII) was prepared by dissolving 0.05 g of the drug in 5 ml of ethanol and bringing the solution to 100.0 ml with water. The lower concentration was used due to its poor water solubility. The standard solutions and mixture of solutions were prepared as needed by diluting the stock solutions with water.

Synthetic Mixture Preparation—A synthetic mixture was prepared by mixing 1.0 g each of I, II, and III and 0.3 g each of V and VII.

Preparation of Assay Solutions of Commercial Dosage Forms and Synthetic Mixture—For VI, an appropriate quantity of the powder representing 10.0 mg of VI was mixed with enough water to bring to 100.0 ml. The mixture was shaken for a few minutes and filtered. The first 15–20 ml of the filtrate was rejected, and a sample was collected for analysis.

For the other compounds, an appropriate quantity of the fine powder was stirred thoroughly with 5 ml of ethanol and brought to 100.0 ml with water. The mixture was filtered, the first 15–20 ml of the filtrate was rejected, and a sample was collected for further dilution. In general, 10.0 ml of the clear filtrate was diluted to 50.0 ml with water. For aspirin-containing products, the solution always was prepared fresh.

The appropriate quantity of the powder required was determined based on the concentrations of various active ingredients in multicomponent dosage forms. In general, the final dilution(s) for analysis contained the following active ingredient concentrations (micrograms per milliliter): I, 30–50; II, 100–250; III, 100–200; V, 15–30; and VII, 30–50. With these concentrations, sensitivity was 0.2 for I and 0.04 for all others. With one commercial dosage form containing I, V, and VII, instead of preparing another dilution for the analysis of VII, a higher concentration (~2.5 times more) was assayed at a sensitivity of 0.1. The standard mixtures used for comparison contained identical or similar concentrations of all active ingredients. The exact ingredient concentrations used for the sample chromatograms are reported in the figures.

Assay—A 20.0-μl aliquot of the assay solution was injected into the chromatograph using the described conditions (Solvent A). An identical volume of the appropriate standard solution or mixture was injected for comparison after the assay solution was eluted. The standard solution or mixture contained identical or similar active ingredient concentrations.

Calculations—Since preliminary investigations indicated that the peak heights (and the peak areas) were directly related to the concentrations tested (in micrograms: I, 0.5–1.2; II, 1.6–6.0; III, 1.6–5.0; V,

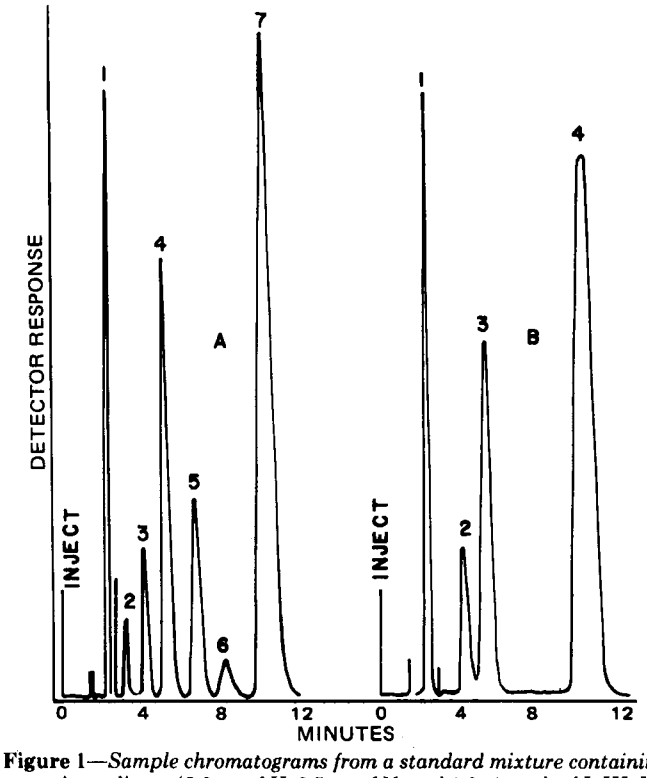

Figure 1—*Sample chromatograms from a standard mixture containing seven ingredients (2.0 μg of II, 0.5 μg of V, and 1.0 μg each of I, III, IV, VI, and VII). Chromatogram A was developed using Solvent A (20% methanol) and chromatogram B was developed using Solvent B. The sensitivity was 0.2 for peak 1 and 0.04 otherwise. The lines after peak 1 indicate the time when the sensitivity was changed. Peaks 1–7 in chromatogram A are from I, VI, III, V, II, IV, and VII, respectively. In chromatogram B, peak 1 is from I, II, and IV; peak 2 is from VI and III; peak 3 is from V; and peak 4 is from VII.*

[1] Waters ALC 202 equipped with a U6K universal injector, Waters Associates, Milford, Mass.
[2] Spectroflow monitor SF770, Schoeffel Instrument Corp., Westwood, N.J.
[3] Omniscribe 5213-12, Houston Instruments, Austin, Tex.
[4] Autolab minigrator, Spectra-Physics, Santa Clara, Calif.
[5] μBondapak C_{18}, catalog No. 27324, Waters Associates, Milford, Mass.
[6] Model 4500 digital pH meter, Beckman Instruments, Irvine, Calif.

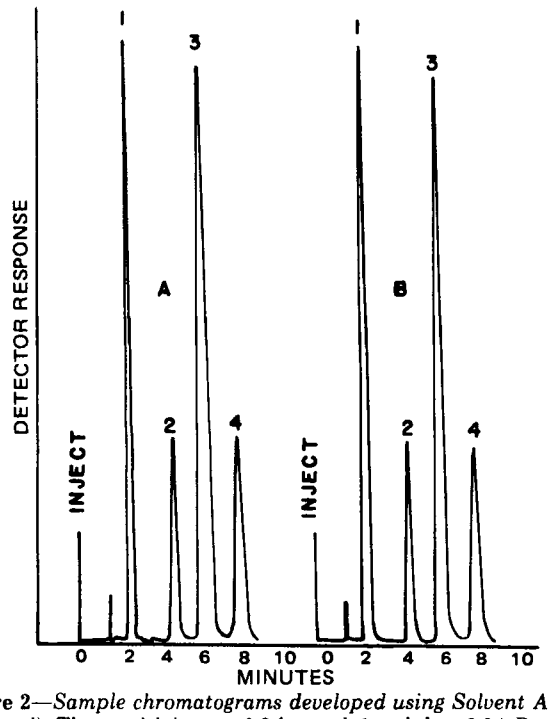

Figure 2—*Sample chromatograms developed using Solvent A (18% methanol). The sensitivity was 0.2 for peak 1 and then 0.04. Peaks 1–4 are from I (0.972 μg), III (1.296 μg), V (0.648 μg), and II (1.944 μg), respectively. Chromatogram A is from a standard mixture, and chromatogram B is from a commercial product.*

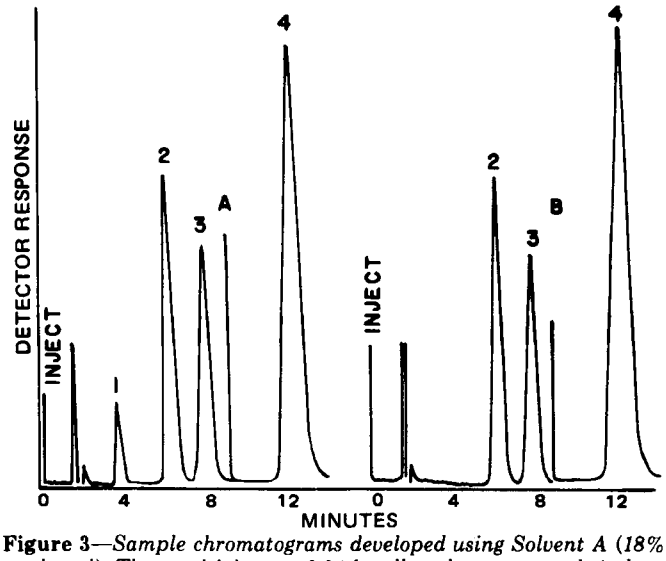

Figure 3—*Sample chromatograms developed using Solvent A (18% methanol). The sensitivity was 0.04 for all peaks except peak 4 where it was 0.1. The lines after peak 3 indicate the time when sensitivity was changed. Peaks 2–4 in both chromatograms are from V, II, and VII, respectively. Peak 1 in chromatogram A is from VI (1.0 μg). The quantities of II, V, and VII injected in chromatogram A (from a standard mixture) were 2.36, 0.32, and 1.56 μg, respectively. In chromatogram B (from a commercial product), the quantities were 2.268, 0.324, and 1.62 μg, respectively.*

0.2–0.7; VI, 1.5–4.0; and VIII, 0.5–1.2), the results were calculated using:

$$\frac{Ph_a}{Ph_s} \times 100 = \% \text{ label claim} \qquad \text{(Eq. 1)}$$

where Ph_a is the peak height of the assay solution and Ph_s is the peak height of the standard.

The ranges given are for a sensitivity of 0.2 for I and 0.04 for all other ingredients. In one commercial sample, VII was assayed using a sensitivity of 0.1. In this assay, peak heights *versus* concentrations were linear between 1.25 and 3.0 μg.

Two sample chromatograms (Fig. 1) were developed by injecting a 20-μl aliquot of a mixture containing 50 μg/ml each of I, III, IV, VI, and VII, 100 μg/ml of II, and 25 μg/ml of V. In the first chromatogram (Fig. 1A), Solvent A containing 20% (v/v) methanol was used; Solvent B (20% methanol) was used in the second chromatogram (Fig. 1B). The results are presented in Table I, and some sample chromatograms are shown in Figs. 2 and 3.

RESULTS AND DISCUSSION

Figure 1A clearly indicates that it is possible to separate seven active ingredients, I–VII, from each other using Solvent A, whose pH was adjusted to 2.3. The same ingredients could not be separated (Fig. 1B) using Solvent B (pH 4.85), which was similar to Solvent A but whose pH had not been adjusted with phosphoric acid. Figure 1B shows only four peaks since aspirin (II) and salicylic acid (IV) were eluted with acetaminophen (I) (peak 1) and codeine phosphate (VI) was eluted with salicylamide (III) (peak 2). The separation between peaks 2 and 3 also was not as good as in Fig. 1A.

By adjusting the solvent pH, the retention times of II and IV were increased and that of VI was decreased, which made the separation possible. Apparently, these changes result because, at a lower pH, both II and IV are predominantly in the undissociated forms while codeine is in the dissociated form. The undissociated forms were expected to be retained for longer times than dissociated forms on a nonpolar column.

With a solvent pH of 2.6–2.7, the retention times of II and IV increased, but these compounds did not separate from one another. It was important to separate these two compounds since IV is the major decomposition product of II. As the pH was decreased, separation became more effective. The pH is very important and functions similar to paired-ion chromatography, in which the retention times are increased.

The analytical results of three commercial dosage forms and a synthetic mixture (Table I and Figs. 2 and 3) indicate that the proposed method can be used for the simultaneous quantitation of active ingredients in various commercial products. Since none of the commercial dosage forms contain all seven ingredients, it is easy to select an internal standard if desired. The peak heights (also peak areas) *versus* concentrations were followed in wide ranges (see *Calculations*). These investigations were not intended to assay IV. Salicylic acid (IV), a major decomposition product of II, was investigated to determine its interference with the analysis of II. It is obvious (Fig. 1A) that it did not interfere. Investigators (11) reported recently that the USP method (12) for the quantitation of II in dosage forms is not stability indicating.

The standard and assay solutions can be prepared in ethanol if desired. Since peak heights vary with the solvent used, both the standard and assay solutions should be prepared in the same solvent. The peak heights were slightly smaller with ethanol as the solvent. Ethanol may be preferred for products containing II since it is less susceptible to hydrolysis in ethanol than in water. The solutions containing II must be prepared immediately before use. Since the optimum stability of II is at about pH 2.3 (13), the mobile phase should have a minimal adverse effect on hydrolysis. With ethanol as the solvent for the assay solution, I did not separate from the ethanol peak. Therefore, ethanol should not be used if I is to be assayed.

The possibilities of assaying very small quantities of IV (0.1% or more) in products containing II are now being studied since USP (12) requires such analysis.

REFERENCES

(1) "Handbook of Nonprescription Drugs," 5th ed., American Pharmaceutical Association, Washington, D.C., 1977, pp. 129–133.

(2) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, pp. 178, 179.

(3) J. R. Leonards, *Clin. Pharmacol. Ther.*, **4**, 476 (1976).

(4) P. A. Harris and S. Riegelman, *J. Pharm. Sci.*, **56**, 713 (1967).

(5) S. Ali, *Chromatographia*, **8**, 33 (1975).

(6) I. L. Honigberg, J. T. Stewart, and M. Smith, *J. Pharm. Sci.*, **67**, 675 (1978).

(7) J. T. Stewart, I. L. Honigberg, and J. W. Coldren, *ibid.*, **68**, 32 (1979).

(8) P. P. Ascione and J. P. Chrekrian, *ibid.*, **64**, 1029 (1975).

(9) G. W. Peng, M. A. F. Gadalla, V. Smith, A. Peng, and W. L. Chiou,

ibid., **67**, 710 (1978).
(10) R. G. Baum and F. F. Cantwell, *ibid.*, **67**, 1066 (1978).
(11) J. R. Luber, A. G. Visalli, and D. M. Patel, *ibid.*, **68**, 780 (1979).
(12) "The United States Pharmacopeia," 19th rev., Mack Publishing Co., Easton, Pa., 1975, pp. 38, 39.
(13) A. N. Martin, J. Swarbrick, and A. Cammarata, "Physical Pharmacy," 2nd ed., Lea & Febiger, Philadelphia, Pa., 1969, p. 388.

High-Pressure Liquid Chromatographic Determination of Salicylic Acid in Aspirin Powder and Pharmaceutical Dosage Forms

V. DAS GUPTA

Received May 10, 1979, from the *Department of Pharmaceutics, College of Pharmacy, University of Houston, Houston, TX 77004.*
Accepted for publication July 31, 1979.

Abstract □ A sensitive, simple, and rapid method for the quantitation of salicylic acid in aspirin powders and its dosage forms was developed. The method is based on reversed-phase high-pressure liquid chromatography using a mobile phase containing 20% methanol in aqueous phosphate buffer of pH 2.3. Other common ingredients present with aspirin such as acetaminophen, caffeine, codeine phosphate, phenacetin, and salicylamide do not interfere. Salicylic acid quantities as low as 0.1 μg can be assayed with a relative standard deviation of ±2.3%. Sensitivity can be increased by using lower sensitivity settings. The method was tried on numerous commercial products and an old aspirin powder. The results generally were excellent, except that all of the aspirin and salicylic acid could not be extracted from suppositories. The old aspirin powder failed the USP limit test for salicylic acid. The powder apparently absorbed moisture and contained salicylamide as an impurity.

Keyphrases □ High-pressure liquid chromatography—analysis, salicylic acid in aspirin powder and dosage forms □ Aspirin—powder and dosage forms, analysis of salicylic acid, high-pressure liquid chromatography □ Salicylic acid—analysis in aspirin powder and dosage forms, high-pressure liquid chromatography

Salicylic acid is the major decomposition product of aspirin. Because free salicylic acid can cause gastric upset, the USP (1) prescribes limit tests for salicylic acid in aspirin powder and in pharmaceutical dosage forms containing aspirin. The limits are 0.1% for aspirin powder, 0.3% for tablets without buffers, 3.0% for buffered aspirin dosage forms, and 1.0% for suppositories. However, the USP method for the quantitation of salicylic acid in aspirin dosage forms is tedious and time consuming. For aspirin powder, the test is qualitative.

A high-pressure liquid chromatographic (HPLC) method (2) was reported which analyzes small aspirin quantities in the presence of large salicylic acid quantities in plasma. However, in dosage forms and aspirin powder, the assay of small salicylic acid quantities in the presence of large aspirin quantities was a problem. A tedious and complicated method was used for the separation of salicylic acid from aspirin (3).

The simultaneous quantitation of acetaminophen, aspirin, caffeine, codeine phosphate, phenacetin, and salicylamide was reported (4). In this method, the salicylic acid did not interfere. Small salicylic acid quantities could not be determined due to a lack of sensitivity in the analytical method. The purpose of these investigations was to develop a simple and rapid HPLC method for the quantitation of small salicylic acid quantities in aspirin powder and its pharmaceutical dosage forms.

EXPERIMENTAL

Reagents and Chemicals—All reagents and chemicals were ACS, USP, or NF quality and were used without further purification.

Apparatus—The high-pressure liquid chromatograph[1] was connected to a multiple-wavelength[2] detector, a recorder[3], and an integrator[4].

Column—The nonpolar column[5] (30 cm × 4 mm i.d.) consisted of a monomolecular layer of octadecyltrichlorosilane permanently bonded by silicone–carbon bonds.

Chromatographic Conditions—The solvent consisted of 0.01 *M* KH_2PO_4 in water with 20% (v/v) methanol, and its pH[6] was adjusted to 2.3 with an 85% aqueous phosphoric acid solution (~1.1 ml/liter). The temperature was ambient. The flow rate was 2.0 ml/min. The detector sensitivity was 0.04 (300 nm), and the chart speed was 30.5 cm/hr.

Solution Preparation—A stock solution of salicylic acid was prepared by dissolving 0.100 g in enough ethanol to bring to 100.0 ml. This solution was diluted with ethanol for the preparation of the standard solution or other solutions.

A stock solution of a standard mixture was prepared by dissolving 48.6 mg of acetaminophen, 97.2 mg of aspirin, 32.4 mg of caffeine, 50.0 mg of phenacetin, 64.8 mg of salicylamide, and 25.0 mg of salicylic acid in 10 ml of ethanol and bringing the solution to 100.0 ml with water. A solution of the standard mixture was prepared by diluting 10.0 ml of the stock solution to 100.0 ml with water. Both the stock and standard mixture solutions were prepared immediately before use.

Preparation of Assay Solutions from Aspirin Powder—All solutions were prepared immediately before injection into the chromatograph. Aspirin powder, 250.0 mg, was dissolved in enough ethanol to bring to 25.0 ml. Another solution of identical strength was prepared from an old aspirin powder (~10 years), which appeared to have decomposed. These solutions were used for the free salicylic acid determination.

Two other aspirin solutions were prepared by diluting the first solution to 250 μg/ml. Solution 1 was prepared by diluting with water, and Solution 2 was prepared with ethanol. These solutions were allowed to stand for ~50 hr and were then analyzed for free salicylic acid. This analysis was done to compare the hydrolysis rate of aspirin in water *versus* ethanol.

Assay Solutions from Solid Dosage Forms—An appropriate quantity of the fine powder was mixed with enough ethanol to bring to 25.0 ml, and the mixture was shaken for 2–3 min and filtered. The first 5–8 ml of the filtrate was rejected, and samples were collected for analysis. The solutions were prepared immediately before analysis. The quantity of the powder weighed represented at least 80 mg (for all nonbuffered tablets) or 50 mg (for buffered tablets) of aspirin. These quantities were determined by considering USP (1) salicylic acid limits. Exact concentrations of the aspirin solutions are reported in Table I.

Suppository Assay Solutions—A suppository containing 600 mg of aspirin was transferred to a 150-ml beaker. The beaker was warmed by

[1] Waters ALC 202 equipped with a U6K universal injector, Waters Associates, Milford, Mass.
[2] Spectroflow monitor SF770, Schoeffel Instrument Corp., Westwood, N.J.
[3] Omniscribe 5213-12, Houston Instruments, Austin, Tex.
[4] Autolab minigrator, Spectra-Physics, Santa Clara, Calif.
[5] μBondapak C_{18}, catalog No. 27324, Waters Associates, Milford, Mass.
[6] Model 4500 digital pH meter, Beckman Instruments, Irvine, Calif.

0022-3549/80/0100-0113$01.00/0