From Eqs. A7 and A9, the overall rate expression of Eq. 6 can be obtained.

REFERENCES

(1) G. N. Rolinson and R. Sutherland, *Adv. Pharmacol. Chemother.*, **11**, 187 (1973).

(2) Y. Ueda, F. Matsumoto, N. Nakamura, A. Saito, K. Noda, C. Furuya, M. Omori, S. Shimojyo, H. Hanaoka, M. Utsunomiya, and T. Fujinoki, *Jpn. J. Antibiot.*, **23**, 48 (1970).

(3) E. A. P. Croydon and R. Sutherland, *Antimicrob. Agents Chemother. –1970,* **1971**, 427.

(4) R. Sutherland, E. A. P. Croydon, and G. N. Rolinson, *Br. Med. J.*, **3**, 13 (1972).

(5) R. C. Gordon, C. Regamey, and W. M. M. Kirby, *Antimicrob. Agents Chemother.*, **1**, 504 (1972).

(6) A. Philipson, L. D. Sabath, and B. Rosner, *ibid.*, **8**, 311 (1975).

(7) J. W. Poole, G. Owen, J. Silverio, J. N. Freyhof, and S. B. Rosenman, *Curr. Ther. Res. Clin. Exp.*, **10**, 292 (1968).

(8) J. P. Hou and J. W. Poole, *J. Pharm. Sci.*, **58**, 1510 (1969).

(9) P. G. Welling, H. Huang, P. A. Koch, W. A. Craig, and P. O. Madsen, *ibid.*, **66**, 549 (1977).

(10) S. A. Hill, K. H. Jones, H. Seager, and C. B. Taskis, *J. Pharm. Pharmacol.*, **27**, 594 (1975).

(11) J. P. Hou and J. W. Poole, *J. Pharm. Sci.*, **58**, 447 (1969).

(12) T. Yamana, A. Tsuji, and Y. Mizukami, *Chem. Pharm. Bull.*, **22**, 1186 (1974).

(13) A. Albert and E. P. Serjeant, "The Determination of Ionization Constants," Chapman and Hall, London, England, 1971.

(14) S. Glasstone and E. F. Hammel, Jr., *J. Am. Chem. Soc.*, **63**, 243 (1941).

(15) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.*, **14**, 329 (1966).

(16) A. H. Goldberg and W. I. Higuchi, *J. Pharm. Sci.*, **57**, 1583 (1968).

(17) S. J. Desai, P. Singh, A. P. Simonelli, and W. I. Higuchi, *ibid.*, **55**, 1224 (1966).

(18) T. Yamana, A. Tsuji, E. Kiya, and E. Miyamoto, *ibid.*, **66**, 861 (1977).

(19) J. W. Poole and C. K. Bahal, *ibid.*, **57**, 1945 (1968).

(20) *Ibid.*, **59**, 1265 (1970).

(21) V. G. Levich, "Physicochemical Hydrodynamics," Prentice-Hall, Englewood Cliffs, N.J., 1962, p. 69.

(22) J. M. Padfield and I. W. Kellaway, *J. Pharm. Pharmacol.*, **27**, 348 (1975).

(23) R. H. Stokes, *J. Am. Chem. Soc.*, **72**, 2243 (1950).

(24) R. N. Bhatia, K. E. Gubbins, and R. D. Walker, *Trans. Faraday Soc.*, **64**, 2091 (1968).

(25) H. R. Bruins, in "International Critical Tables," vol. 5, E. W. Washburn, Ed., McGraw-Hill, New York, N.Y., 1929, p. 68.

(26) H. S. Harned and W. J. Hammer, *J. Am. Chem. Soc.*, **55**, 2194 (1933).

(27) D. A. Wadke and G. E. Reier, *J. Pharm. Sci.*, **61**, 868 (1972).

(28) R. Broderson, *Trans. Faraday Soc.*, **43**, 351 (1947).

(29) A. Hussain, *J. Pharm. Sci.*, **61**, 811 (1972).

(30) P. L. Whyatt, G. W. A. Slywka, A. P. Melikian, and M. C. Meyer, *ibid.*, **65**, 652 (1976).

(31) W. I. Higuchi, E. L. Parrott, D. E. Wurster, and T. Higuchi, *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 376 (1958).

ACKNOWLEDGMENTS

Presented in part at the 97th annual meeting of the Pharmaceutical Society of Japan, Tokyo, Japan, April 1977.

The authors acknowledge the gifts of amino penicillins from Takeda Chemical Industries and Sankyo Co. They also thank Mr. W.-Z. Hwang and Miss H. Yamazaki for technical assistance.

Determination of Salicylic Acid and Aspirin in Multicomponent Tablets by Liquid Chromatography on a Nonionic Resin

ROBERT G. BAUM and FREDERICK F. CANTWELL ˣ

Received September 26, 1977, from the *Department of Chemistry, University of Alberta, Edmonton, Alberta, Canada T6G 2G2.* Accepted for publication November 18, 1977.

Abstract □ Aspirin and free salicylic acid were determined in combinations containing caffeine, phenacetin, salicylamide, and acetaminophen by liquid chromatography on poly(methyl methacrylate) resin. Precision and accuracy were ±0.6% for aspirin and ±2% for salicylic acid, the latter at levels corresponding to 0.02% of the aspirin content.

Keyphrases □ Aspirin—liquid chromatographic analysis in multicomponent tablets □ Salicylic acid—liquid chromatographic analysis in multicomponent tablets □ Liquid chromatography—analyses, aspirin and salicylic acid in multicomponent tablets □ Analgesics—aspirin and salicylic acid, liquid chromatographic analyses in multicomponent tablets

Of the methods reported for the determination of aspirin and salicylic acid in pharmaceutical preparations, relatively few permit their simultaneous determination. Partition chromatography combined with spectrophotometric measurement has been used for free salicylic acid determination in aspirin products (1–3). Direct spectrophotometry (4) and fluorometric methods (5, 6) also have been used for free salicylic acid determination.

The simultaneous determination of aspirin and salicylic acid has been performed by UV spectrophotometry (7), but this method and methods based on IR spectrophotometry (8) and nonaqueous titration (9) all lack sensitivity for the low levels of salicylic acid present in freshly prepared aspirin tablets. The simultaneous determination of aspirin and salicylic acid based on fluorometric or colorimetric quantitation has been performed on a continuous-flow automated analyzer (10).

GLC separation of aspirin and salicylic acid was achieved on high molecular weight polyethylene glycol containing isophthalic acid and supported on glass microbeads (11). Salicylic acid eluted after aspirin and showed considerable tailing, precluding use of the method for free salicylic acid in tablets. The presence of active

0022-3549/ 78/ 0800-1066$01.00/ 0

© 1978, American Pharmaceutical Association

hydrogens on the carboxyl and phenolic groups requires derivative formation to obtain well-defined GLC peaks (12–14).

Salicylic acid and aspirin were separated by high-performance liquid chromatography on a pellicular strong base anion exchanger at a mobile phase pH of 9.2 (15, 16). Salicylic acid was much more strongly retained than aspirin, but no quantitative data were presented. The two compounds were separated on silica gel adsorbents with various mobile phases (14, 17, 18), and free salicylic acid was determined in aspirin formulations (14).

In the present study, the chromatographic column was packed with a macroporous poly(methyl methacrylate) resin[1] (19). This inexpensive adsorbent has been found useful for the liquid chromatographic analysis of multicomponent analgesic formulations (20). The goal of the present work was the development of a rapid simultaneous chromatographic assay for aspirin and its principal impurity and decomposition product, salicylic acid, in multicomponent analgesic tablets.

EXPERIMENTAL

Apparatus—The liquid chromatograph was assembled from commercially available components (Fig. 1). Two solvent delivery pumps, P1[2] and P2[3], were employed. Glass chromatographic columns[4] were dry packed with <325-mesh macroporous resin. The precolumn, C1, was 5 × 0.28 cm; the analytical column, C2, was 15 × 0.28 cm. The photometric detector was either a UV absorbance detector set at 280 nm[5] or a variable wavelength UV–visible detector[6]. All fittings and polytef tubing were supplied by one manufacturer[7].

The precolumn was connected into the system *via* a rotary injection valve, V1[8], in such a way that, in one valve setting (shown in Fig. 1 as dashed lines), P1 pumped Solvent 1 through the precolumn and the analytical column. At the same time, P2 pumped Solvent 2 to waste. In this configuration, 20 μl of sample solution was injected onto the precolumn by the slider injection valve, V2[9].

After aspirin and salicylic acid eluted from the precolumn, but before any of the other drug components eluted, V1 was switched to the position shown by the solid lines. With V1 in this position, Solvent 1 still flowed through the analytical column, while the precolumn was removed from series and washed with Solvent 2. Immediately after switching V1, the detector sensitivity was changed from 0.01 to 0.64 aufs. To minimize extracolumn band broadening in the polytef tubing associated with V1 and V2, the 0.8-mm i.d. tubing supplied with the valves was replaced with 0.3-mm i.d. tubing.

Chemicals and Reagents—Aspirin[10] and salicylic acid[10] were analyzed by USP methods (1) as 100.0 and 99.6%, respectively. Other drugs and tablet excipients were USP or equivalent grade. Hexane and ethanol were anhydrous reagent grade and were distilled before use. Ether, acetic acid, and dioxane were reagent grade and were used as received.

All mobile phase solvents were prepared volumetrically by transferring measured volumes of a given solvent into a volumetric flask and diluting to volume with hexane. Solvent 1 was 25% ether–10^{-2} M acetic acid in hexane. Solvent 2 was 50% ethanol in hexane.

The preparation of <325-mesh resin was described previously (20). The acid washing step in this procedure is necessary to reduce aspirin and salicylic acid tailing.

Tablets, Blank, and Synthetic Mixture—Tablets were purchased at a local pharmacy. The average tablet weight was determined (21), for each product and the tablets were ground to a fine powder. Sample solutions were prepared by weighing a quantity of powdered tablets equivalent to 250 mg of aspirin into 25-ml volumetric flasks, shaking with 10.0 ml of dioxane, and diluting to volume with hexane. Undissolved solids were filtered out by drawing the solution into the sampling valve through a small plug of cotton placed in the inlet tubing.

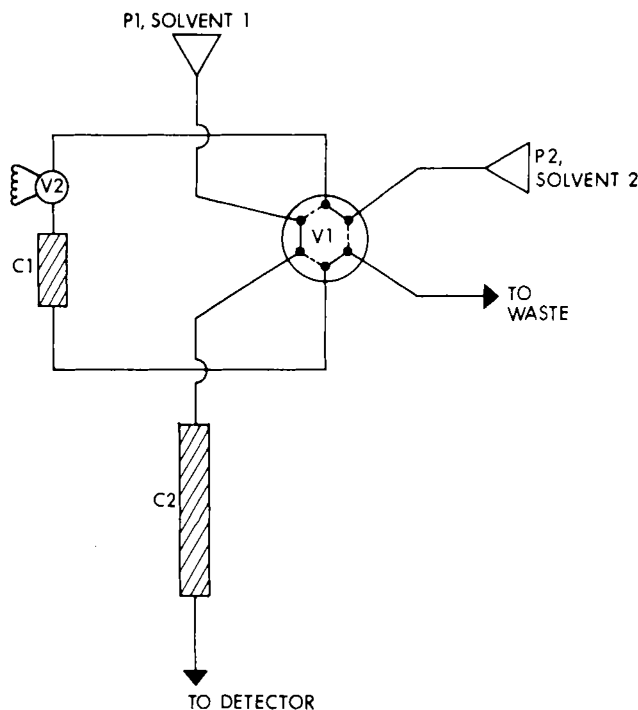

Figure 1—*Diagram of the liquid chromatograph.*

To demonstrate the lack of chromatographic interference by common tablet excipients and likely active ingredients, a blank mixture was prepared containing corn starch, talc, lactose, stearic acid, caffeine, phenacetin, salicylamide, and acetaminophen. A blank solution was prepared by shaking this mixture with dioxane and diluting with hexane as for tablet samples. Quantitative recovery of aspirin and salicylic acid was demonstrated by chromatographing a dioxane–hexane solution of a synthetic mixture containing known amounts of aspirin and salicylic acid along with salicylamide, phenacetin, caffeine, and acetaminophen.

Tablets and the synthetic mixture were analyzed for aspirin and salicylic acid by comparison of peak heights to calibration curves. Calibration curves were obtained by injecting mixtures of the two compounds containing 8.8–11 mg of aspirin/ml and 0.002–0.0065 mg of salicylic acid/ml dissolved in 40% dioxane–hexane. A 20-μl sampling valve was used for all injections. The peak height due to salicylic acid already present in the aspirin was measured by injecting a standard solution of aspirin, and this value was subtracted from that of the standard mixtures to obtain the peak height due to added salicylic acid.

RESULTS AND DISCUSSION

Chromatographic Behavior—Although the detailed mechanism of adsorption of sample molecules on this polyacrylate resin has not yet been elucidated, it is useful to view the resin as a relatively nonpolar adsorbent. Sample molecules interact with the resin *via* dispersion forces, dipole forces, and hydrogen bonding. Mobile phase solvent molecules also interact with the resin and compete with sample molecules for adsorption sites on the resin surface.

A third type of interaction is that between sample molecules and solvent molecules. In contrast to the situation that prevails when using polar adsorbents such as silica gel, it is not possible to neglect the influence of this third type of interaction on the chromatographic retention of a sample molecule. No eluotropic series exists for the nonpolar resin. In fact, it has been shown that for several analgesics the retention volume varies inversely with the solubility of the drug in the mobile phase solvent (20).

Plots of the net retention volumes for five analgesics and salicylic acid *versus* the percent ether in an ether–hexane mobile phase already were presented (20). Previous publications (20, 22) showed how this type of plot may be used to select column length and mobile phase composition to achieve the desired retention and resolution of sample components. Application of this approach to the present problem suggests that base-

[1] Amberlite XAD-7, Rohm & Haas Co., Philadelphia, Pa.
[2] Model CMP-2VK, Laboratory Data Control, Riviera Beach, Fla.
[3] Syringe pump, Perkin-Elmer Corp., Norwalk, Conn.
[4] Type MB, Laboratory Data Control, Riviera Beach, Fla.
[5] Model 230, Spectra Physics, Santa Clara, Calif.
[6] Model 770, Schoeffel Instrument Corp., Westwood, N.J.
[7] Laboratory Data Control, Riviera Beach, Fla.
[8] Model R6031 SVP, Laboratory Data Control, Riviera Beach, Fla.
[9] Model CSV, Laboratory Data Control, Riviera Beach, Fla.
[10] Baker Chemical Co., Phillipsburg, N.J.

Table I—Net Retention Volumes on a 20 × 0.28-cm Column of Macroporous Resin

Compound	Net Retention Volume in	
	25% Ether[a]	25% Ether–10^{-2} M Acetic Acid
Salicylic acid	2.0	1.84
Aspirin	7.8	6.05
Phenacetin	41	34.2
Salicylamide	44	39.4
Caffeine	100	47.0
Acetaminophen	>150	>150

[a] Values calculated from data in Ref. 20.

line resolution between salicylic acid and the unretained solvent peak and between aspirin and salicylic acid can be achieved on a 20 × 0.28-cm column using 25% ether in hexane as the mobile phase. Predicted retention volumes are given in Table I. Theoretical plate heights calculated on the basis of the six compounds, studied at linear velocities of 0.25 cm/sec, were between 0.1 and 0.17 cm; the void volume for a 20-cm column was 1.7 ml.

With an ether–hexane mobile phase, salicylic acid was the first compound of the six to elute, which is desirable for chromatographic trace analysis (23).

To minimize tailing of aspirin and salicylic acid peaks, 10^{-2} M acetic acid was added to the 25% ether mobile phase. The presence of acetic acid had the side effect of reducing the net retention volumes of the six compounds compared to their net retention volumes in 25% ether (Table I). The greatest effect of added acetic acid was on the retention volume of the basic compound caffeine. Retention volumes of salicylic acid and aspirin were affected slightly, and the difference in retention volumes between aspirin and phenacetin, salicylamide, caffeine, and acetaminophen remained very large (Table I).

Because of the large retention volumes of the other drugs, it would be necessary to wait an inordinately long time between sample injections to elute strongly retained components. On the other hand, if these strongly retained components were not allowed to elute between sample injections, they would produce severely drifting baselines as they eluted during later sample chromatograms. One solution to this problem would be a change to a strong eluent such as 50% ethanol in hexane after the elution of aspirin (20). However, the analysis time then would be prolonged both by the time required to elute the strongly retained components with the stronger solvent and by the time required to reequilibrate the resin with 25% ether–10^{-2} M acetic acid before making the next injection.

An alternative approach, adopted in this study, is to employ a short column of resin located in series before the analytical column (Fig. 1). With this configuration, the sample solution is injected into the chromatograph with Solvent 1 as the mobile phase. Valve V1 is switched after aspirin has eluted from the precolumn but before any of the other four drugs has eluted from the precolumn. After V1 is switched to the position shown with solid lines in Fig. 1, the salicylic acid and aspirin continue to chromatograph down the analytical column with Solvent 1 mobile phase; the strong eluent Solvent 2 passes through the precolumn, washing off the more strongly retained components. After aspirin has eluted through the detector, V1 is put back to its original setting, and a 5-min equilibration period is allowed before the next injection. The total time between injections is about 15 min.

If the sample contains salicylamide or phenacetin, a small fraction of it may elute from the precolumn along with aspirin and salicylic acid, depending upon precisely when valve V1 is switched. This occurrence presents no problem, however, since these compounds are well resolved from aspirin on the 15-cm column with Solvent 1, and they are eluted completely by the "slug" of ethanol-rich solvent that passes through it when the precolumn is switched back into series.

Analysis of Tablets—Linear calibration curves of peak height at 280 nm *versus* milligrams of compound per milliliter of solution were obtained for both aspirin and salicylic acid. Slopes of the calibration curves were 0.037 and 0.22 absorbance unit/mg/ml for aspirin and salicylic acid, respectively, with relative average deviations for replicate injections of 0.6 and 2%, respectively. In the absence of aspirin, salicylic acid had a slightly longer retention time and a peak height about 14% smaller than when aspirin was present. However, as long as some aspirin was present, the salicylic acid peak was insensitive even to large variations in the amount of aspirin. For this reason, the standards used to construct the calibration curve were mixtures of the two compounds. The presence of other drugs had no effect on the shapes of either the aspirin or salicylic acid peak.

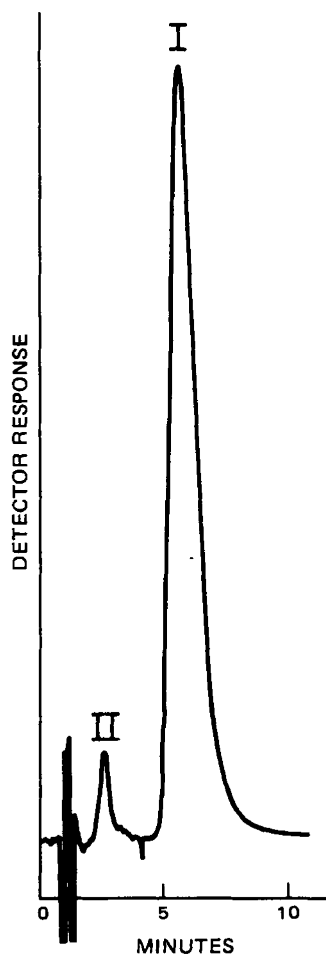

Figure 2—*Typical chromatogram for an aspirin (I) tablet containing 0.028% free salicylic acid (II). The conditions were: pressure, 420 psig; flow rate, 1.35 ml/min; linear velocity, 0.26 cm/sec; detector wavelength, 280 nm; and detector sensitivity, 0.01 aufs for II and 0.64 aufs for I.*

To assess the accuracy of the method, a synthetic mixture containing known amounts of aspirin and salicylic acid, along with salicylamide, phenacetin, caffeine, and acetaminophen, was prepared as already described and analyzed. Assay results for this sample as well as for several commercial tablet preparations are summarized in Table II. Results for the latter are reported on the basis of average tablet weight for each product. The fifth column in Table II gives the salicylic acid as a percentage of the aspirin found in the tablet. Quantitative recovery was observed for both aspirin and salicylic acid in the synthetic mixture. The salicylic acid content of all commercial tablets fell well within the USP limit of 0.3%.

A typical chromatogram of a tablet preparation found to contain 0.090 mg of salicylic acid/tablet and 320 mg of aspirin/tablet is presented in Fig. 2. The negative spike between the salicylic acid and aspirin peaks occurred when the precolumn was taken out of series by switching valve V1.

A problem with all determinations of free salicylic acid in aspirin tablets is the relatively rapid hydrolysis of aspirin in solution to produce additional salicylic acid. Usually, the analysis must be performed as soon as possible after dissolving the sample. In the present method, the salicylic acid concentration increased linearly in the dioxane–hexane sample solutions over at least 5 hr. The generation rate of salicylic acid ranged from 3×10^{-5} mg/ml/hr in Tablet B to 2.4×10^{-4} mg/ml/hr in Tablet A, with the other tablet batches having values between these. All solutions contained 10 mg of aspirin/ml. Thus, if one prepares the standard and sample solution within about 15 min of the injection time, the error in the free salicylic acid determination will be negligible. For the highest accuracy, samples and standards can be chromatographed at various times after preparing their solutions and the results can be extrapolated to zero time. This method was used for the data in Table II.

For comparison with the present method, Tablets A and C were analyzed for free salicylic acid by the official USP method (21). Standards were chosen to bracket the salicylic acid content of the tablets so that quantitative assay values could be obtained. Tablet A contained 0.12 ± 0.005 mg/tablet and Tablet C contained 0.080 ± 0.007 mg/tablet by the USP method. These values are in agreement with those reported in Table II.

Table II—Assay Results for Tablets and Synthetic Mixture

Product	Aspirin, mg/Tablet Label Claim	Aspirin, mg/Tablet Found	Salicylic Acid, mg/Tablet Found	Salicylic Acid, %	Other Drugs Present
A[a]	325	331	0.115	0.035	—
B[b]	325	320	0.090	0.028	—
C[c]	324	323	0.074	0.023	—
D[d]	455	454	0.153	0.034	—
E[e]	455	449	0.082	0.018	Caffeine
F[f]	455	447	0.190	0.043	Caffeine
G[g]	325	310	0.178	0.057	Salicylamide
Synthetic[h] mixture	—	219 (218)	0.126 (0.128)	0.059	Caffeine, phenacetin, acetaminophen, salicylamide

[a] Bayer Aspirin (lot 116NO), Bayer Co., Division of Sterling Drug Ltd., Aurora, Ontario, Canada. [b] Safeway A.S.A. (lot C62A BB), Wes-Pak Products Ltd., North Vancouver, British Columbia, Canada. [c] Lifeprin (lot B48A BA), Stanley Drug Products Ltd., North Vancouver, British Columbia, Canada. [d] Instantine (lot 0920K), Bayer Co., Division of Sterling Drug Ltd., Aurora, Ontario, Canada. [e] Anacin (lot 916 VC), Whitehall Laboratories Ltd., Toronto, Ontario, Canada. [f] C 2 Tablets (lot 154071), Wampole Ltd., Perth, Ontario, Canada. [g] Excedrin (lot 047), Bristol-Meyers Canada Ltd., Toronto, Ontario, Canada. [h] Amount in parentheses is amount added.

The proposed chromatographic method for salicylic acid is significantly more precise and sensitive than the current USP method. This advantage can be further increased by using a detector wavelength nearer the UV absorption maximum of salicylic acid (Fig. 3). At 312 nm, the salicylic acid peak height was over twice its value at 280 nm. The aspirin peak was very small at this wavelength, but this problem can be overcome readily by using a detector sensitivity greater than 1.00 aufs.

Although wavelengths higher than 280 nm appear to be preferable for the analysis of salicylic acid and aspirin, they are not available on most commercial UV absorbance detectors; for this reason, the commonly available wavelength of 280 nm was employed. For comparison, a chromatogram recorded at 254 nm is also included in Fig. 3. This detector wavelength is the most commonly available, but it is considerably less sensitive than 280 nm for detecting salicylic acid.

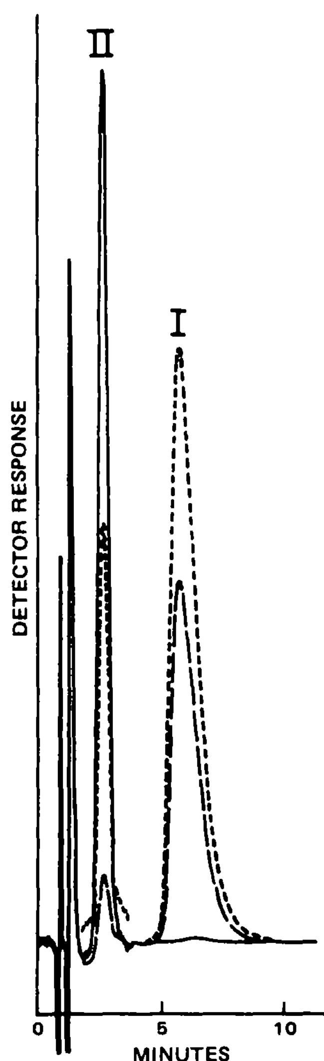

Figure 3—*Chromatogram for a standard solution containing 0.013 mg of salicylic acid (II)/ml and 9.9 mg of aspirin (I)/ml. Detector wavelengths were 254 (- -), 280 (---), and 312 (—) nm. Detector sensitivity was 0.01 aufs for II and 1.00 for I. Other conditions were as in Fig. 2.*

This method is significantly faster than the USP XIX method for free salicylic acid, and its speed can be increased further by packing the resin in steel columns and using higher pressures to achieve higher mobile phase flow rates. The precolumn is not necessary when analyzing products containing aspirin as the only active ingredient.

REFERENCES

(1) J. D. Weber and J. Levine, *J. Pharm Sci.*, **55**, 78 (1966).
(2) J. Levine and J. D. Weber, *ibid.*, **57**, 631 (1968).
(3) D. E. Guttman and G. W. Salomon, *ibid.*, **58**, 120 (1969).
(4) R. C. Reed and W. W. Davis, *ibid.*, **54**, 1533 (1965).
(5) N. Shane and D. Miele, *ibid.*, **59**, 397 (1970).
(6) N. Shane and R. Stillman, *ibid.*, **60**, 114 (1971).
(7) A. W. Clayton and R. E. Thiers, *ibid.*, **55**, 404 (1966).
(8) G. Kister, M. Ribes, J. Chanal, and A. Catterini, *Ann. Pharm. Fr.*, **34**, 215 (1976).
(9) S.-L. Lin, *J. Pharm. Sci.*, **56**, 1130 (1967).
(10) H. Kubin and H. Gaenshirt, *Pharm. Ind.*, **38**, 224 (1976).
(11) J. G. Nickelly, *Anal. Chem.*, **36**, 2248 (1964).
(12) J. R. Watson, P. Crescuolo, and F. Matsui, *J. Pharm. Sci.*, **60**, 454 (1971).
(13) S. Patel, J. H. Perrin, and J. J. Windheuser, *ibid.*, **61**, 1794 (1972).
(14) S. L. Ali, *J. Chromatogr.*, **126**, 651 (1976).
(15) R. A. Henry and J. A. Schmit, *Chromatographia*, **3**, 116 (1970).
(16) J. A. Schmit, in "Modern Practice of Liquid Chromatography," J. J. Kirkland, Ed., Wiley-Interscience, New York, N.Y., 1971, p. 388.
(17) P. P. Ascione and G. P. Chrekian, *J. Pharm. Sci.*, **64**, 1029 (1975).
(18) K. Harzer and R. Barchet, *Dtsch. Apoth.-Ztg.*, **116**, 1229 (1976).
(19) "Preliminary Technical Notes: Amberlite XAD-7," Rohm & Haas Co., Philadelphia, Pa., 1972.
(20) R. G. Baum and F. F. Cantwell, *Anal. Chem.*, **50**, 280 (1978).
(21) "The United States Pharmacopeia," 19th Rev., Mack Publishing Co., Easton, Pa., 1975.
(22) H. Y. Mohammed and F. F. Cantwell, *Anal. Chem.*, **50**, 491 (1978).
(23) J. J. Kirkland, *Analyst (London)*, **99**, 859 (1974).

ACKNOWLEDGMENTS

Supported by the National Research Council of Canada and the University of Alberta.