Rapid Quantitative Determination of Three Active Ingredients in Liquid Antitussive Preparations by High-Speed Liquid Chromatography

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Abstract □ Three active ingredients in liquid antitussive preparations, acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide, were separated by high-speed liquid chromatography on an octadecylsilane (permanently bonded to a controlled surface porosity support) column with a buffered, pH 8.8, alcohol-water mobile phase and measured with a UV photometer. Due to the relatively large excess of acetaminophen and the fixed detector wavelength (254 nm), the analysis was performed sequentially in two steps. Nonetheless, results were obtained in one-third the time required for conventional methods and instrument flexibility was maintained, thereby permitting its use for a variety of analyses. The relative standard deviations for the three components were 1.8, 0.76, and 2.0%, respectively.

Keyphrases □ Acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide mixtures—high-speed liquid chromatographic separation and UV analysis □ Chlorpheniramine maleate, acetaminophen, and dextromethorphan hydrobromide mixtures—high-speed liquid chromatographic separation and UV analysis □ Dextromethorphan hydrobromide, acetaminophen, and chlorpheniramine maleate mixtures—high-speed liquid chromatographic separation and UV analysis □ Antitussive mixtures (acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide)—separation, analysis □ High-speed liquid chromatography—separation, UV analysis, acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide mixtures □ UV spectrophotometry—analysis, acetaminophen, chlorpheniramine maleate, and dextromethorphan hydrobromide mixtures after high-speed liquid chromatographic separation

Chromatography, which originated with Day (1) and Tswett (2), first was reported in 1900–1903. Until recently, liquid chromatography was of limited utility to the analytical chemist because of lengthy analysis time and relatively poor column efficiency. The potential for rapid analysis of single- and multicomponent formulations was attained when commercial instrumentation and new column materials became available (3–8). Although optimum operating conditions, maximum efficiency, and qualitative separation of various components have been described (9–14), reports of quantitative determinations, specifically on pharmaceutical preparations, are lacking.

The analyses of acetaminophen, chlorpheniramine maleate, dextromethorphan hydrobromide, and similar components have been performed utilizing partition (15, 16), ion-exchange[1] (17), and gas (18) chromatography. The objective of this study was to develop, on a practical basis, a more rapid and precise method for these three compounds. This report describes the successful application of high-speed liquid chromatography to the quantitative determination of these components, an amide and two amines, in commercial antitussive preparations.

[1] Quality control procedure, Hoffmann-La Roche Inc., Nutley, NJ 07110

EXPERIMENTAL[2]

Instrumentation—A liquid chromatograph[3], having a pressure capability of 3000 psig, was equipped with a UV precision photometer and a differential refractometer for detection, a fraction collection valve, a degassing unit, a thermostatically controlled oven, and a gradient elution accessory. Two recorders[4] were employed. The UV detector had a fixed measuring wavelength at 254 nm. The sample cell volume was approximately 7 μl, and the cell path was 8.6 mm. Samples were injected with a 5-μl syringe[5]. UV spectra were obtained with a recording spectrophotometer[6].

Reagents and Chemicals—The following were used: alcohol[7] (anhydrous 3A), alcohol[7] USP, chloroform[8], boric acid[8], potassium chloride[8], sodium chloride[8], sodium sulfate[9] (anhydrous granular), and ammonium hydroxide[10].

A pellicular cation-exchange column packing[11] was employed for preliminary experimental studies.

Determination of Acetaminophen—*Column and Conditions*—Stainless steel, precision bore tubing, 100 cm × 6.35 mm o.d. × 2.1 mm i.d., was packed with octadecylsilane[12] chemically bonded to the surface of a controlled surface porosity support[13] and containing approximately 1% stationary phase (octadecylsilane) by weight. The instrument operating conditions for this column (Column A) were: pressure, ~1800 psig; flow rate, ~0.65 ml/min; oven temperature, ambient; injection volume, 5 μl; and chart speed, 0.75 in./min.

Preparation of Mobile Phase—Weigh accurately 6.184 g of boric acid into a 1-liter volumetric flask and dissolve in 297 ml of water. Add 0.5 ml of concentrated hydrochloric acid and 2.5 ml of concentrated ammonium hydroxide. Dilute with approximately 650 ml of alcohol USP, mix well, adjust to pH 9.0 with concentrated hydrochloric acid or ammonium hydroxide, and bring to the final mark with alcohol USP.

Preparation of Standard Solutions—Internal Standard: Weigh accurately 10 mg of reference amitriptyline hydrochloride into a 10-ml volumetric flask. Dissolve and dilute to volume with the mobile phase.

Reference Standard: Weigh accurately 25 mg of acetaminophen reference standard into a 10-ml volumetric flask. Dissolve and dilute to volume with water, (Standard Solution I). Dilute 4 ml of Standard Solution I to 100 ml with the mobile phase (Standard Solution II).

Working Standard Solution: Into a small vial, pipet 1.0 ml of reference Standard Solution II and 1.0 ml of the internal standard solution. Stopper and mix thoroughly.

Sample Preparation—Accurately transfer a sample aliquot equivalent to approximately 50 mg of acetaminophen into a 100-ml volumetric flask. Dilute to volume with distilled water and mix thoroughly (Sample Solution I).

Transfer a 10-ml aliquot of Sample Solution I into a 50-ml volumetric flask, dilute to volume with the mobile phase, and mix thoroughly (Sample Solution II).

Into a small vial, pipet 1.0 ml of Sample Solution II and 1.0 ml

[2] All reference standards were obtained from Hoffmann-La Roche Inc., Nutley, NJ 07110
[3] Du Pont Instruments, model 820.
[4] Honeywell Electronic 194 and Texas Instrument Servo-Riter, 0–1 mv.
[5] Hamilton High-Pressure, model HP 305 N.
[6] Cary model 14.
[7] Publicker Industries Inc.
[8] Merck reagent grade.
[9] Mallinckrodt.
[10] J. T. Baker Chemical Co.
[11] Pellex CP 122, Northgate Laboratories, Hamden, Conn.
[12] Permaphase ODS (Catalog No. 820951001), E. I. du Pont & Co.
[13] Zipax, E. I. du Pont & Co.

Table I—Reproducibility of the Response Ratios for Multiple Injections of a Single Solution

Component	Response Ratio	Mean	Standard Deviation	Relative Standard Deviation
Acetaminophen	3.533	3.584	±0.0475	±1.3%
	3.645			
	3.557			
	3.633			
	3.592			
	3.542			
Chlorpheniramine maleate	0.2870	0.2935	±0.0054	±1.8%
	0.2997			
	0.2880			
	0.2915			
	0.2987			
	0.2961			
Dextromethorphan hydrobromide	0.01666	0.01648	±0.00018	±1.1%
	0.01655			
	0.01627			
	0.01641			
	0.01671			
	0.01630			

Table II—Comparative Analyses of Three Active Ingredients in a Single Cough Preparation[a]

	Acetaminophen[b]		Chlorpheniramine Maleate[c]		Dextromethorphan Hydrobromide[d]	
Sample	HSLC[e]	Ion-Exchange Method[f]	HSLC[e]	Ion-Exchange Method[f]	HSLC[e]	Ion-Exchange Method[f]
1	126	123	1.00	0.98	16.0	15.1
2	120	121	1.01	1.00	15.8	15.1
3	124	122	1.03	1.01	16.3	15.1
4	126	124	1.00	1.05	14.7	15.5
5	126	124	1.03	1.04	15.2	15.3

[a] Results in mg/5 ml are the average of duplicate determinations. [b] Label claim: 120 mg/5 ml. [c] Label claim: 1.00 mg/5 ml. [d] Label claim: 15.0 mg/5 ml. [e] High-speed liquid chromatography. [f] Data obtained in a separate laboratory using the manual ion-exchange method.

of the internal standard solution. Stopper and mix thoroughly (working sample solution).

Chromatographic Analysis—Equilibrate the column with the mobile phase at ambient temperature and inject 5 µl of the working standard solution. Acetaminophen is eluted first, followed by amitriptyline. A typical chromatogram for acetaminophen on the octadecylsilane-bonded column is shown in Fig. 1. After the amitriptyline is eluted, the column is ready for another injection. (The septum should be changed after approximately six injections.) All peak areas are obtained from an electromechanical (disk) or electronic digital integrator. Repeat the injection of the standard solution until a reproducible response ratio is obtained and then chromatograph the working sample solution.

Calculations—For the determination of the response ratio of acetaminophen:

$$R_N \text{ (acetaminophen response ratio)} = \frac{A_N \text{ (standard)} \times C_A}{A_A \text{ (standard)} \times C_N} \quad \text{(Eq. 1)}$$

where:

A_N = acetaminophen peak area of the standard
A_A = amitriptyline peak area of the standard
C_N = concentration of acetaminophen in milligrams per milliliter of working standard solution
C_A = concentration of amitriptyline hydrochloride in milligrams per milliliter of working standard

For the analysis of acetaminophen in the antitussive preparation:

$$\frac{A_N \text{ (sample)} \times C_A \times 5000}{A_A \text{ (sample)} \times R_N \times S} = \frac{\text{mg acetaminophen/5 ml}}{\text{antitussive preparation}} \quad \text{(Eq. 2)}$$

where A designates area, C is concentration, and R_N is the response ratio as calculated in Eq. 1; 5000 = dilution factor and conversion to 5 ml; and S = sample aliquot taken for analysis.

Determination of Dextromethorphan Hydrobromide and Chlorpheniramine Maleate—*Column Conditions*—The following conditions were employed: column, octadecylsilane bonded to a controlled surface porosity support (Column A); pressure, ~1900 psig; flow rate, ~1.5 ml/min; oven temperature, 50° (and reservoir); injection volume, 5 µl; and chart speed, 0.75 in./min.

Preparation of Mobile Phase—Buffer Solution (0.2 *M* potassium chloride and 0.2 *M* boric acid): Weigh accurately 12.37 g of boric acid and 14.91 g of potassium chloride into a 1-liter volumetric flask. Dissolve and dilute to volume with water.

Mobile Phase: Transfer 100 ml of buffer solution into a 1-liter volumetric flask. Add 399 ml of distilled water and 0.2 ml of concentrated ammonium hydroxide. Dilute with approximately 450 ml of 3A alcohol, mix well, adjust to pH 8.8, and bring to the final mark with 3A alcohol.

Preparation of Standard Solution—Internal Standard: Weigh accurately 45 mg of chlorprothixene into a 100-ml volumetric flask. Dissolve and dilute to volume with alcohol USP.

Reference Standard: Weigh accurately 100 mg of reference chlorpheniramine maleate and 1.50 g of reference dextromethorphan hydrobromide into a 100-ml volumetric flask. Dissolve and dilute to volume with water.

When chlorpheniramine maleate is not present in the sample, the standard should be prepared by weighing 750 mg of reference dextromethorphan hydrobromide into a 100-ml volumetric flask and dissolving and diluting to volume with water.

Working Standard Solution: Transfer 2.0 ml of reference standard solution into a 125-ml separator. Add 28 ml of water and mix thoroughly. From this point, handle exactly as for the *Extraction Procedure* of the sample solution.

Sample Preparation—For products containing only dextromethorphan hydrobromide, quantitatively transfer, with the aid of 20 ml of water and using a suitable volumetric flask, an aliquot of antitussive preparation equivalent to approximately 15 mg of dextromethorphan hydrobromide into a 125-ml separator.

For products containing both chlorpheniramine maleate and dextromethorphan hydrobromide, quantitatively transfer, with

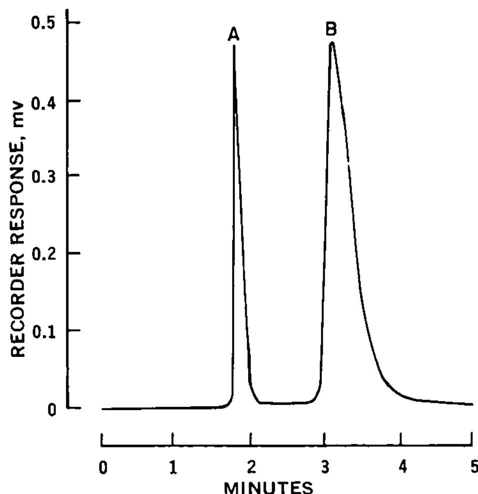

Figure 1—*Separation of acetaminophen (A) and amitriptyline (B) on the permanently bonded octadecylsilane column at an attenuation of 32× (0.32 absorbance unit full-scale).*

the aid of 20 ml of water and using a suitable volumetric flask, an aliquot of antitussive preparation equivalent to approximately 2 mg of chlorpheniramine maleate and 30 mg of dextromethorphan hydrobromide into a 125-ml separator.

The amount of water used for the transfer will depend on the quantity of the sample taken for analysis, and the alcohol content of the preparation.

Extraction Procedure—Add 3 g of sodium chloride to the separator, dissolve, and make the solution strongly basic with 10 ml of concentrated ammonium hydroxide. Extract with 3 × 40 ml of chloroform (if emulsions are encountered, the quantity of chloroform can be increased). Transfer the chloroform layers into a 250-ml separator, combine, and wash until neutral with 3 × 50 ml of distilled water. Pass the chloroform layer through a funnel containing 25 g of anhydrous granular sodium sulfate into a 250-ml erlenmeyer flask, and then wash the sodium sulfate with an additional 15 ml of chloroform. Evaporate the chloroform to dryness under a flow of nitrogen on a steam bath. Dissolve a residue in 2.0 ml of the internal standard solution (working sample solution).

Chromatographic Analysis—Equilibrate the column with the mobile phase at 50° (oven and reservoir temperature). A temperature of 60° should be used for analysis of products containing only

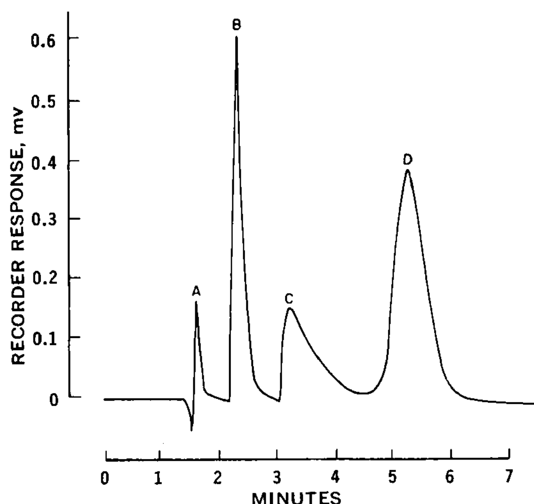

Figure 2—*Separation of chlorpheniramine, dextromethorphan, and chlorprothixene at an oven temperature of 50° and attenuation of 16× (0.16 absorbance unit full-scale) on the permanently bonded octadecylsilane column. Key: A, instrument dead volume; B, chlorpheniramine; C, dextromethorphan; and D, chlorprothixene.*

Table III—Comparative Precision Data

Compound	Standard Deviation, mg		Relative Standard Deviation, %	
	Ion-Exchange Method[a]	HSLC[b]	Ion-Exchange Method[a]	HSLC[c]
Acetaminophen	±1.3	±2.3	±1.05	±1.83
Dextromethorphan hydrobromide	±0.27	±0.31	±1.72	±1.99
Chlorpheniramine maleate	±0.009	±0.008	±0.93	±0.76

[a] Data obtained in a separate laboratory using the manual ion-exchange method. [b] High-speed liquid chromatography. Pooled standard deviation using results from Table II. [c] High-speed liquid chromatography. Pooled coefficient of variation.

dextromethorphan. Adjust the pressure to obtain a flow rate of 1.5 ml/min and inject 5 μl of the working standard solution. Chlorpheniramine, which is eluted after the dead volume, is followed by dextromethorphan and chlorprothixene (Fig. 2).

After the chlorprothixene is eluted completely, the column is ready for another injection. (The septum should be changed after approximately six injections.) All peak areas are obtained from an electromechanical (disk) or electronic digital integrator. Repeat the standard solution until a reproducible response ratio is obtained and then chromatograph the working sample solution.

Calculations—For the determination of the response ratio for dextromethorphan hydrobromide and chlorpheniramine maleate:

$$R_D = \frac{A_D \text{ (standard)} \times C_T}{A_T \text{ (standard)} \times C_D} \quad \text{(Eq. 3)}$$

$$R_C = \frac{A_C \text{ (standard)} \times C_T}{A_T \text{ (standard)} \times C_C} \quad \text{(Eq. 4)}$$

where:

A_D or A_C = dextromethorphan or chlorpheniramine peak area of the standard
A_T = chlorprothixene peak area of the standard
C_D or C_C = concentration of dextromethorphan hydrobromide or chlorpheniramine maleate in milligrams per milliliter of the working standard solution
R_D or R_C = dextromethorphan hydrobromide or chlorpheniramine maleate response ratio
C_T = concentration of chlorprothixene in milligrams per milliliter of the working standard solution

For the analysis of dextromethorphan hydrobromide or chlorpheniramine maleate in the antitussive preparation:

$$\frac{A_D \text{ (sample)} \times C_T \times 10}{A_T \text{ (sample)} \times R_D \times S} = \text{mg dextromethorphan hydrobromide/5 ml antitussive preparation} \quad \text{(Eq. 5)}$$

$$\frac{A_C \text{ (sample)} \times C_T \times 10}{A_T \text{ (sample)} \times R_C \times S} = \text{mg chlorpheniramine maleate/5 ml antitussive preparation} \quad \text{(Eq. 6)}$$

where A designates area, C is concentration, and R is the respective response ratio as calculated in Eqs. 3 and 4; 10 = dilution factor and conversion to 5 ml; and S = sample aliquot taken for analysis.

RESULTS AND DISCUSSION

Column and Mobile Phase Selection—Preliminary experiments indicated that qualitative separation of the three components could be obtained on a pellicular cationic column, which is a logical choice for these types of compounds. Reasonable peak

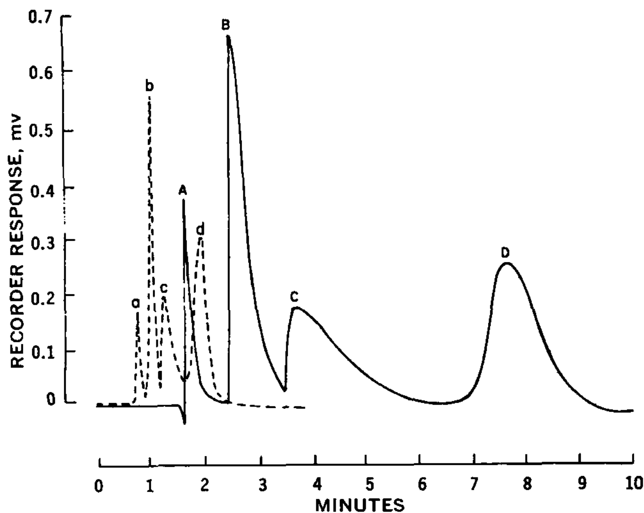

Figure 3—*Separation of chlorpheniramine, dextromethorphan, and chlorprothixene at an oven temperature of 30° (16×, 0.16 absorbance unit full-scale) and 70° (32×, 0.32 absorbance unit full-scale) on the permanently bonded octadecylsilane column. Key (30°, 70°): A, a, instrument dead volume; B, b, chlorpheniramine; C, c, dextromethorphan; and D, d, chlorprothixene.*

shapes for the three compounds in the salt form were achieved during a single chromatographic analysis but, due to the relatively large excess of acetaminophen, complete resolution from the other two components was not obtained.

Direct injection of the syrups was also not feasible since it resulted in interferences and unreproducible chromatograms. Therefore, it was necessary to determine acetaminophen after dilution of the sample with water, while the other two components were analyzed following extraction from an alkaline solution. Quantitative determinations for acetaminophen were carried out, and results equal to the label claim were obtained. When assays were performed for the other two components in their base form on the pellicular cation-exchange column, poor reproducibility, approximately ±10%, was obtained; consequently, a partition chromatographic approach was evaluated.

The behavior of the three components was investigated on an octadecylsilane, permanently bonded to a controlled surface po-

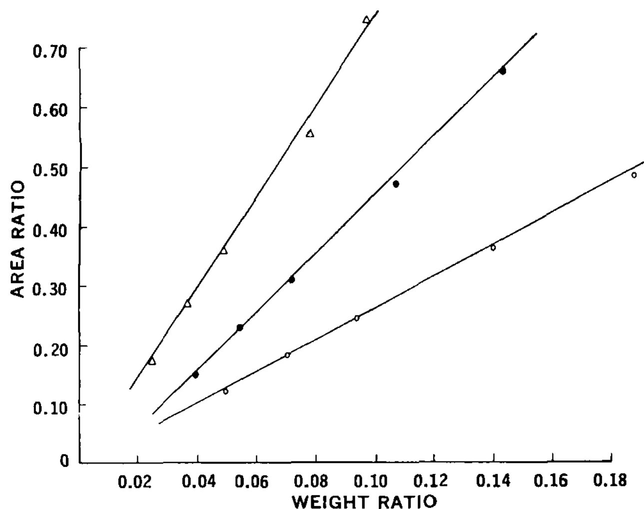

Figure 4—*Standard curves for acetaminophen with amitriptyline as the internal standard, chlorpheniramine with chlorprothixene as the internal standard, and dextromethorphan with chlorprothixene as the internal standard. Key: O, acetaminophen; Δ, chlorpheniramine (area ratio × 2:weight ratio × 5); and ●, dextromethorphan (area ratio × 2:weight ratio × 500).*

Table IV—Concentration of the Components in the Analyzed Antitussive Preparations as Shown in the Tables

Product	Components	Claim
A	Dextromethorphan hydrobromide	15 mg/5 ml
	Chlorpheniramine maleate	1 mg/5 ml
	Acetaminophen	120 mg/5 ml
	Fluidextract of ipecac	0.005 ml/5 ml
	Chloroform	0.25%
	Alcohol	10%
B	Dextromethorphan hydrobromide	7.5 mg/5 ml
	Sodium citrate	
	Menthol	
C	Dextromethorphan hydrobromide	5 mg/5 ml
	Chlorpheniramine maleate	0.34 mg/5 ml
	Acetaminophen	100 mg/5 ml
	Phenylephrine hydrochloride	1.7 mg/5 ml
	Alcohol	25%
D	Dextromethorphan hydrobromide	Quantitative statement not available
	Chlorpheniramine maleate	
	Acetaminophen	
	Ephedrine sulfate	
	Alcohol	25%

rosity, solid-core microbead column which had the following advantages: a nonextractable chemically bonded organic polymeric stationary phase and commercial availability of uniformly packed columns (8).

Permanently bonded octadecylsilane is nonpolar and, therefore, a polar mobile phase (alcohol-water) was the appropriate choice. While the mobile phase previously used for acetaminophen on the pellicular cation-exchange column also was suitable for acetaminophen on the octadecylsilane-bonded column, it did not yield a good resolution for chlorpheniramine maleate and dextromethorphan hydrobromide. Since previous studies did not indicate the mechanism of separation (9) and since a minor alteration of the mobile phase could result in changes in selectivity, a study of suitable mobile phases was initiated. Experiments indicated that a slightly buffered solution was preferable and confirmed, as reported elsewhere (13), that an elevated temperature improved the separation. The elevated temperature decreased solvent viscosity, decreased band broadening, and provided more symmetrical peak shapes by apparently increasing the rate of mass transfer (Fig. 3). Considering these factors, the desirable mobile phase was a mixture of 0.02 *M* potassium chloride and 0.02 *M* boric acid in 50% 3A alcohol, adjusted to pH 8.8 with ammonium hydroxide.

Internal Standard and Retention Times—To minimize apparatus and injection errors, a study was performed to select an internal standard. After screening 35 compounds, amitriptyline hydrochloride was found to be suitable as the internal standard for the analysis of acetaminophen. The retention times were 1.9 min for acetaminophen and 3.2 min for amitriptyline. While acetaminophen has the same retention time as the dead volume, interference was not encountered from any excipient. In addition, the use of the mobile phase for sample preparation minimized any contribution from the solvent to the total area at this retention time. Chloride ion was necessary in the mobile phase for reproducible elution of the amitriptyline.

The most suitable internal standard for the analysis of chlorpheniramine maleate and dextromethorphan hydrobromide was chlorprothixene, which exhibited a retention time of 5.2 min compared to chlorpheniramine at 2.3 min and dextromethorphan at 3.2 min. The initial peak at 1.7 min was attributed to the instrumental response for any unretained component. Ephedrine, if present, will elute between chlorpheniramine and dextromethorphan at a retention time of 2.7 min. Phenylephrine did not interfere.

Response and Linearity—To ascertain the coincidence of the UV absorption maxima of the measured compounds with the instrument setting of 254 nm and to determine the effect of the mo-

Table V—Determination of Acetaminophen, Chlorpheniramine Maleate, and Dextromethorphan Hydrobromide in Liquid Antitussive Preparations

Product	Component	Found, mg/5 ml	Percent Claim
A	Dextromethorphan hydrobromide	15.3	102
	Chlorpheniramine maleate	1.04	104
	Acetaminophen	124	103
B	Dextromethorphan hydrobromide	7.6	101
C	Dextromethorphan hydrobromide	5.0	100
	Chlorpheniramine maleate	0.37	109
	Acetaminophen	101.5	101.5
D	Dextromethorphan hydrobromide	3.0	—[a]
	Chlorpheniramine maleate	0.42	—[a]
	Acetaminophen	105	—[a]

[a] Quantitative statement not available.

bile phase on the spectra, complete UV curves were recorded. The peak maxima for all three compounds did not coincide with 254 nm. The total absorption at 254 nm for dextromethorphan hydrobromide was approximately 10% of the peak maximum value at 280 nm, which accounted for the necessity to overload the column and the resultant tailing peak. The other two compounds exhibited UV absorptions at 254 nm equivalent to approximately 85% of their maximum intensity values.

Response *versus* concentration curves for each compound demonstrated that sample concentration was linear with area and that elution times were reproducible (within 1–2% relative to the respective average retention times).

Five different concentrations of acetaminophen, ranging from 0.12 to 0.48 μg, were injected. Figure 4 shows varying ratios of acetaminophen standard solutions *versus* amitriptyline, plotted as relative area per relative concentration. The symmetrical peaks permitted accurate measurements of area, and the data fitted a straight-line plot.

The same procedure was followed for chlorpheniramine maleate and dextromethorphan hydrobromide. An area *versus* concentration curve for each compound employing chlorprothixene as the internal standard is shown in Fig. 4, and the data fitted a straight-line plot in the concentration range studies.

Instrument Repeatability and Recovery—After column conditions were defined, instrument precision was evaluated. Multiple injections of a single solution of each compound indicated that the relative standard deviation of the response ratio was between 1 and 2% (Table I).

Chloroform proved to be the best extraction solvent for these compounds (19). Sodium chloride was added because, in the presence of chloride ion, chloroform would extract dextromethorphan readily regardless of the pH (15). Extraction recoveries carried out for the two amines, with standards analyzed in exactly the same manner to minimize any extraction loss due to handling, yielded results comparable to the label claim. When the extracted samples were compared to unextracted standards, lower levels (90–95%) were obtained.

Sample Analysis—Duplicate assays were performed, as described under the *Experimental* section, on six lots of one antitussive preparation. Results agreed with the label claims for all three components (Table II). The relative standard deviations were comparable to those reported for the manual ion-exchange method (Table III). In addition, four commercial antitussive preparations were analyzed using this method. The concentration of the components and the results are listed in Tables IV and V.

CONCLUSION

Although all possible combinations of instrument and column conditions were not thoroughly explored, an efficient separation of three active ingredients in commercial antitussive preparations was realized. Interference was not observed due to the presence of excipients or other active ingredients such as phenylephrine hydrochloride and ipecac fluidextract. Ephedrine sulfate, after extraction as ephedrine from an alkaline medium, was eluted between chlorpheniramine and dextromethorphan; but at the level present in the preparation studied, it did not interfere with the measurement of the other peaks.

As observed in this study and as previously reported (10), high-speed liquid chromatography is restricted by the limited peak capacity which results from the noncoincidence of the UV absorption maximum of the component and the available detector wavelength.

Although the liquid chromatographic method did not completely eliminate the sample preparation steps, the results of the analysis of six samples of one antitussive preparation showed that operator analysis time can be reduced from approximately 12 hr/lot for the manual ion-exchange method[1] to approximately 4 hr/lot. In conjunction with the reduction in analysis time, instrument flexibility was maintained, thereby permitting its use for a variety of analyses.

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