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ION-PAIR HIGH-PERFORMANCE LIQUID CHROMATOGRAPHIC DETERMINATION OF CHLORPHENIRAMINE MALEATE IN COUGH-COLD MIXTURES

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ABSTRACT

A high-performance liquid chromatographic method in the ion-pair mode was developed for the assay of chlorpheniramine maleate in commercial cough-cold mixtures. The method uses a μBondapak phenyl column and a mixture of acetonitrile-acetic acid-water (26.5:1.0:72.5, by volume, pH 2.4) containing 0.005M pentanesulfonic acid sodium salt as the mobile phase. Chlorpheniramine maleate was well resolved from ten other active ingredients. A linear relationship was obtained between detector response at 254 nm and amounts of chlorpheniramine maleate injected ranging from 0.8 to 2.5 μg(r=0.996). A reproducibility study using a standard preparation gave a CV of 1.43% (n = 10). The average recovery values of chlorpheniramine maleate added in various amounts to a single-component tablet composite sample and to a multiple-component tablet composite sample were 99.1 and 100.9%, respectively. The assay of commercial tablets by the proposed method gave

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results which differed by 0.7 to 3.2% of declared from those obtained by the method of USP XX.

INTRODUCTION

The USP XX assay method for chlorpheniramine maleate in tablets consists of multiple extraction steps followed by an ultraviolet spectrophotometric determination (1). This method is only designed for single component dosage forms. Reported high-performance liquid chromatographic (HPLC) methods for chlorpheniramine maleate have been applied to its mixtures with other antihistamines (2-4) or to cough-cold combinations containing from two to four active ingredients (5-12). The HPLC method presented here permits the separation and quantitative determination of chlorpheniramine maleate in tablets containing combinations of this drug with any one or all of the following: isopropamide, phenylephrine, phenylpropanolamine, pseudoephedrine, acetaminophen, phenacetin, guaiafenesin, aspirin, caffeine, and dextromethorphan.

EXPERIMENTAL

Materials and Reagents - Single-component and multiple-component tablets containing chlorpheniramine maleate were obtained from commercial sources. All HPLC solvents and reagents were used as obtained: Acetonitrile[1], acetic acid[1], and pentanesulfonic acid sodium salt[2]. The mobile phase was prepared by mixing acetonitrile, acetic acid, and water (26.5:1.0:72.5, by volume) to which enough pentanesulfonic acid sodium salt was added to yield a 0.005M solution. The solution was mixed with a few drops of sulfuric acid to bring its pH to 2.4, and degassed prior to use by sonication under vacuum.

Standard Solution - An accurately weighed 25 mg quantity of chlorpheniramine maleate[3] was placed in a 250 ml volumetric flask, mixed with about 50 ml of mobile phase and sonicated for 15 minutes. The solution was diluted to volume with mobile phase, mixed, and filtered through a medium speed filter paper[4]. The first portions of filtrate were discarded.

Sample Preparation - Determine the average weight of 20 tablets. Grind the tablets in a mortar and pestle, until the total powdered composite passes through a 60 mesh sieve[5]. Mix the powder thoroughly, and transfer an accurately weighed quantity, equivalent to 5 mg of chlorpheniramine maleate, to a 50 ml volumetric flask. Add 20 ml of mobile phase and sonicate for 15 minutes. Dilute to volume with mobile phase, and mix. Filter the solution through a medium speed filter paper, discarding the first portions of filtrate.

Chromatograph - The liquid chromatograph consisted of a single pump attached to a spectrophotometric detector and a strip-chart recorder[6]. Using a 20 µl loop injector[7], sample preparations and standard solutions were introduced into a 30 cm x 3.9 mm i.d. stainless steel column packed with 10 μm particle size μBondapak phenyl[8]. Chromatography was conducted at ambient temperature using a flow rate of 0.75 ml/min, a chart recorder speed of 1.0 cm/min, and a detector set at 254 nm and a sensitivity of 32 AUFS. **The quantity of chlorpheniramine maleate per** tablet was obtained from peak height measurements and the following equation:

$$\text{mg/tablet} = (H_u/H_s) \times C \times D \times (A/W)$$

where H_u = peak height of the sample, H_s = peak height of the standard, C = concentration of the standard preparation, mg/ml, D = dilution factor of the sample, A = average tablet weight, mg/tab, and W = amount of sample composite taken for analysis, mg.

RESULTS AND DISCUSSION

Figures 1 and 2 show typical HPLC separations of chlorpheniramine maleate from other active ingredients found in commercial cough-cold tablets. Table 1 gives the retention times for this drug and for ten additional active components studied. In the event that the high concentration of any given component affects the resolution of chlorpheniramine, it will be necessary to dilute the sample further until a satisfactory separation is obtained. Alternatively, the same result may be obtained by varying the proportion of acetonitrile in the mobile phase.

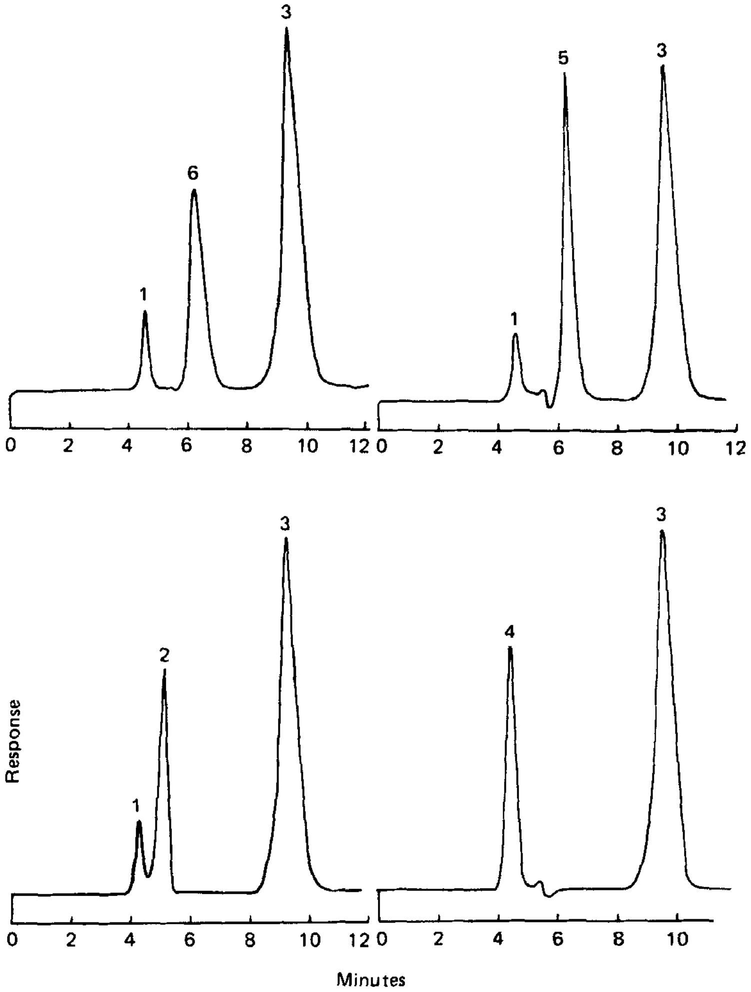

Figure 1 - High-pressure liquid chromatograms of synthetic binary mixtures. Key: 1. maleic acid (from chlorpheniramine maleate); 2. phenylephrine; 3. chlorpheniramine; 4. isopropamide; 5. acetaminophen; 6. pseudoephedrine.

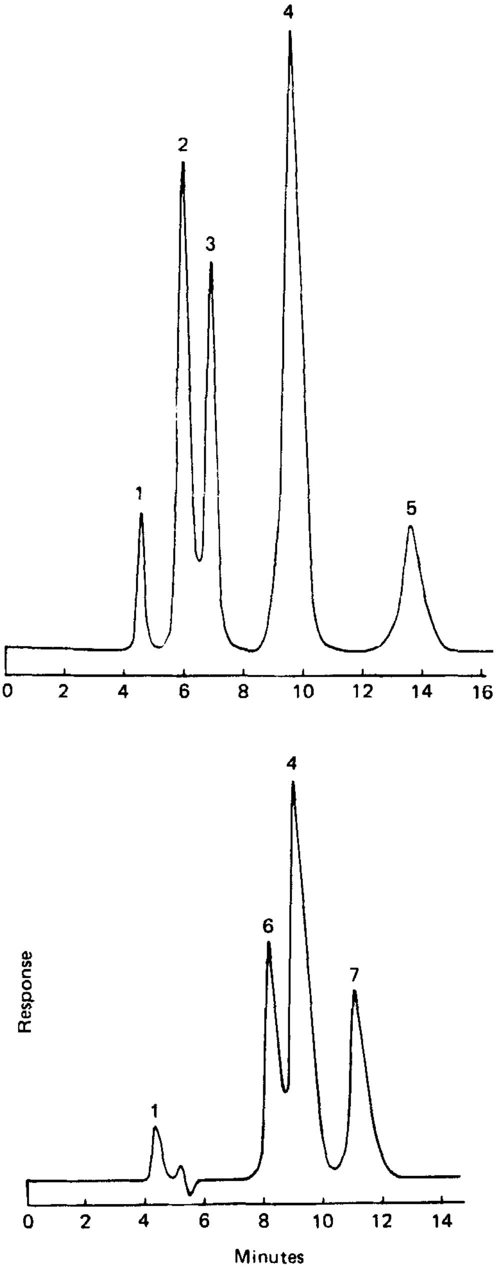

Figure 2 - High-pressure liquid chromatograms of ternary and quaternary synthetic mixtures. Key: 1. maleic acid (from chlorpheniramine maleate); 2. phenylpropanolamine; 3. phenacetin; 4. chlorpheniramine; 5. caffeine; 6. guaifenesin; 7. aspirin.

Table 1 - Retention Times for Chlorpheniramine Maleate and Ten Additional Active Ingredients Found in Cough-Cold Mixtures

Compound	Amount in the mixture, mg/ml[a]	Retention Time, min
Isopropamide	3.000	4.35
Phenylephrine hydrochloride	0.400	5.10
Phenylpropanolamine	2.000	5.90
Pseudoephedrine sulfate	2.000	6.20
Acetaminophen	0.020	6.30
Phenacetin	0.008	6.85
Guaiafenesin	0.400	8.20
Chlorpheniramine maleate	0.200	9.30
Aspirin	0.400	11.10
Caffeine	0.040	13.60
Dextromethorphan hydrobromide	1.000	22.00

[a] Injected as a mixed standard preparation dissolved in the mobile phase.

Table 2 indicates that the proposed method is linear over the range of 0.816 to 2.448 μg of chlorpheniramine maleate injected (r=0.996). A reproducibility study based on peak height measurements for ten consecutive injections of a standard preparation of chlorpheniramine maleate gave a CV of 1.43% (Table 3). The average recovery of chlorpheniramine maleate added to single-component and to multiple-component tablet composite samples in the

Table 2 - Linearity of Detector Responses versus Concentrations of Chlorpheniramine Maleate Injected

Amount injected, μg	No. of injections	Peak height av. ± SD, mm
2.448	4	155.6 ± 1.6
1.632	3	116.0 ± 4.0
1.224	3	89.3 ± 1.2
0.816	3	62.0 ± 4.6

Table 3 - Reproducibility of Peak Heights for Ten Successive Injections of a Standard Preparation Containing 0.0612 μg/μl

Statistical parameter	Value
Range, mm	82.0 - 85.5
Average, mm	83.05
SD, mm	1.18
CV, %	1.43

Table 4 - Recovery of Chlorophenirамine Maleate from Commercial Tablet Composites

Sample	Amount found, mg	Amount added, mg	Total found, mg	Recovery, %	Av. recovery, %
Single-component tablet	1.480	3.528	4.990	99.5	99.1
	1.003	4.032	4.954	98.0	
	0.505	4.536	5.026	99.7	
Multiple component tablet[a]	0.395	1.075	1.493	102.1	100.9
	0.247	1.229	1.472	99.7	

[a] Sample preparation containing 0.03 mg/ml; detector sensitivity, 0.04 AUFS; mobile phase containing 16% of acetonitrile. Other components present: acetaminophen, 325 mg/tab; phenylpropanolamine HCl, 12.5 mg/tab; dextromethorphan HBr, 10 mg/tab.

Table 5 - Average Assay Results for Chlorpheniramine Maleate Tablets by the HPLC and USP XX methods

		Found[a]			
		HPLC		USP XX	
Sample	Declared, mg/tablet	mg/tablet	% of declared	mg/tablet	% of declared
A	4	4.00	100.0	4.05	101.3
B	4	3.77	94.3	3.87	96.8
C	4	4.02	100.5	3.98	99.5

[a] Each is the average of 2 determinations

concentrations listed in Table 4 were 99.1 and 100.9%, respectively.

Samples of commercial tablets containing chlorpheniramine maleate in combination with other active ingredients were assayed for chlorpheniramine maleate by both the proposed method and the USP XX method for Chlorpheniramine Maleate Tablets. As shown in Table 5, differences in assay values between these two methods, ranged from 0.7 to 3.2% of declared.

In addition to being more rapid and specific than the compendial spectrophotometric method, the HPLC method presented here will permit the determination of chlorpheniramine maleate in combination dosage forms containing up to ten additional drug substances.

ACKNOWLEDGMENTS

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FOOTNOTES

1. Fisher Scientific Co., Fairlawn, NJ
2. Altex Scientific Inc., Berkeley, CA

3. Schering Corporation, Kenilworth, NJ
4. Whatman No. 40 or equivalent, Whatman Laboratory Products Inc., Clifton, NJ
5. Dual Manufacturing Co., Chicago, IL
6. Model 950 pump, Model 970A detector, Tracor Instruments, Inc., Austin, TX
7. Rheodyne Inc., Cotati, CA
8. Waters Associates, Inc., Milford, PA

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