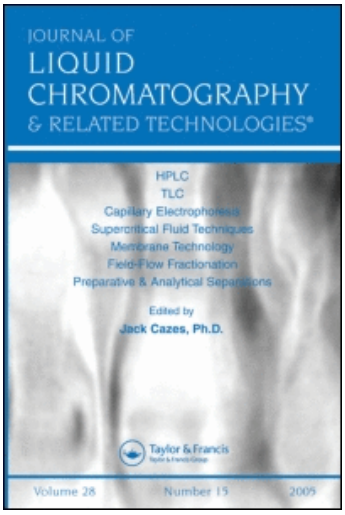

Journal of Liquid Chromatography & Related Technologies
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597273

Quantitative Determination of Guaifenesin, Phenylprolamine Hydrochloride Sodium Benzoate Δ Codeine Phosphate in Cough Syrups by High-Pressure Liquid Chromatography

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To cite this Article Muhammad, Naseem and Bodnar, Joy A.(1980) 'Quantitative Determination of Guaifenesin, Phenylprolamine Hydrochloride Sodium Benzoate Δ Codeine Phosphate in Cough Syrups by High-Pressure Liquid Chromatography', Journal of Liquid Chromatography & Related Technologies, 3: 1, 113 — 122
To link to this Article: DOI: 10.1080/01483918008060158
URL: http://dx.doi.org/10.1080/01483918008060158

JOURNAL OF LIQUID CHROMATOGRAPHY, 3(1), 113-122 (1980)

QUANTITATIVE DETERMINATION OF GUAIFENESIN, PHENYLPROPANOLAMINE HYDROCHLORIDE SODIUM BENZOATE & CODEINE PHOSPHATE IN COUGH SYRUPS BY HIGH-PRESSURE LIQUID CHROMATOGRAPHY

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ABSTRACT

A rapid paired-ion high-pressure liquid chromatographic method for the quantitative determination of guaifenesin, phenylpropanolamine hydrochloride, sodium benzoate and codeine phosphate in cough syrups was developed. Heptane sulfonic acid was used as a counter-ion in the mobile phase. A fixed wavelength detector (λ = 254 nm) and a μ-Bondapak phenyl column was employed. Total analysis time for all the active ingredients was 22 minutes.

INTRODUCTION

Cough syrups are complex mixtures which contain several active ingredients along with several excipients such as dyes, preservatives, flavors and sweeting agents. Gas chromatography and high-pressure liquid chromatography have been used for their analysis. Mario and Meecham [1] review the problem involved in quantitative analysis of active ingredients of cough syrups. In the case of GLC assay methods, an initial liquid-liquid extraction of the drugs from the aqueous syrup is required to eliminate water and, sometimes, interfering excipients [2,

1). After extraction, the polar compounds are derivitized before gas chromatography. The liquid chromatographic behavior of a number of active ingredients present in cough syrups on non-polar bonded phases has been reported. The syrups, with their potentially interfering excipients, were not analyzed and amine compounds showed considerable tailing (3, 4). Other methods involved non-aqueous titration (5), conductometric titrations (6), spectrophotometry (7), and column and thin-layer chromatography (5, 8). Recently, a liquid chromatographic analysis of pharmaceutical syrups using pre-columns and salt-adsorption on Amberlite XAD-2 has been reported (9).

Paired-ion high-pressure liquid chromatography has become popular for increasing the retention times of weak acids and bases by the addition of a counter-ion to the mobile phase. Alkyl sulfonates are used for basic compounds and quaternary ammonium compounds are used for acid compounds (10). In the present study, an assay method is described for the quantitative determination of guaifenesin, phenylpropanolamine hydrochloride, sodium benzoate and codeine phosphate present in commercial dosage forms used to relieve the symptoms of coughs and colds. The assay method is based on paired-ion HPLC with sodium heptane sulfonate as the counter-ion. The preparation of samples is simple and rapid since the drugs can be analyzed in their salt forms. Separation and analysis times require less than 25 minutes.

EXPERIMENTAL

Reagents:

Methanol, Burdick & Jackson, Muskegon, MI, Spectrophotometer Grade.

1-Heptane Sulfonic Acid Sodium Salt, Eastman Chemical Company, Rochester, New York.

Glacial Acetic Acid, Reagent Grade A.C.S.

p-Hydroxyphenoxy-acetic acid, Eastman Chemical Company, Rochester, New York.

Guaifenesin, Phenylpropanolamine·HCl, Sodium Benzoate and Codeine Phosphate, (Reference Standards) Bristol Laboratories, Syracuse, New York.

HPLC Conditions:

Column:	*μ-Bondaphenyl (3.9 mm ID x 30 cm) from Waters Associates, Milford, Mass., P/N 27198.*
Pump:	*Waters 6000A or equivalent.*
Mobile Phase:	*MeOH/Water (36/62) each with 0.004M 1-Heptane Sulfonic Acid, Sodium Salt and 1% Glacial Acetic Acid or equivalent.*
Flow Rate:	*0.5 ml/minute, or equivalent.*
Injector:	*Valco Loop Injector, 7000 psi, 20-μl loop, Valco Instrument Co., Inc., Houston, Texas.*
Detector:	*Waters Model 440 or equivalent, 254 nm.*
Chart Speed:	*0.5 inch/minute.*

Suggested Attenuations & Retention Times:	*RT (min.)*	*Attenuations*
p-OH Phenoxyacetic Acid (p-OH POAc)	*9.40*	*1.0*
Guaifenesin	*15.02*	*1.0*
Phenylpropanolamine·HCl	*16.70*	*0.1*
Sodium Benzoate	*18.30*	*0.1*
Codeine Phosphate	*20.35*	*0.1*

Mobile Phase Preparation:

Into a 200-ml volumetric flask, add 180 mg of 1-Heptane Sulfonic Acid Sodium Salt and 2.00 ml of acetic acid. Dilute to volume with methanol.

Into a 500-ml volumetric flask add 450 mg of 1-Heptane Sulfonic Acid Sodium Salt, add 5.00 ml of acetic acid, and dilute to volume with distilled water. Combine 190 ml of the methanol solution with

310 ml of the aqueous solution to make 500 ml of mobile phase. Stir and degas gently for 15 seconds. *It is important that the methanol portion of the mobile phase be prepared fresh daily and that any standards or samples diluted with mobile phase be prepared fresh daily*.

With the variability in columns, it may be necessary to modify the mobile phase to achieve the separation between Sodium Benzoate and Codeine or between Phenylpropanolamine and Guaifenesin. To do this, increase the distilled water ratio in the mobile phase.

Internal Standard Preparation:

Weigh accurately approximately 2.0 g of p-Hydroxyphenoxy-acetic Acid into a 50-ml volumetric flask. Dilute to volume with mobile phase.

Standard Preparation:

Weigh accurately approximately 200 mg of Guaifenesin into a 50-ml volumetric flask.

Weigh accurately approximately 25 mg of Sodium Benzoate, 50 mg of Codeine Phosphate, and 90 mg of Phenylpropanolamine HCl into a 25-ml

Standard Preparation, Cont'd.

volumetric flask. Dilute to volume with mobile phase. Add 5.00 ml into the 50-ml volumetric flask containing the guaifenesin. Add 5.00 ml of internal standard solution into the 50-ml volumetric flask. Dilute to volume with mobile phase.

Sample Preparation:

Pipet 5.00 ml of syrup into a 50-ml volumetric flask. Add 5.00 ml of the internal standard solution. Dilute to volume with mobile phase.

Calculations:

Measure the area by the peak height x half-width method or by computer.

1) Factor (F) = $\frac{\text{mg/ml of active ingredient x area internal std.}}{\text{mg/ml of internal std. x area of active ingredient}}$

2) Sample

mg of active ingredient/5 ml of syrup =

$$\frac{\text{Area of active ingredient x mg/ml int. std. x F x 50}}{\text{Area of internal standard}}$$

RESULTS & DISCUSSION

The purposes of this work were to determine the operating conditions for paired-ion HPLC that would optimize resolution of the four active ingredients commonly found in the cough syrups in a reasonable time and to quantitate the analysis with a suitable level of precision.

The parameters that were varied during this study were: (a) concentration of methanol and water both containing .004M sodium heptane sulfonate; (b) flow rate, and (c) polarity of the reversed stationary phase. The effects of these parameters on the separation of the drugs studied is shown in Table 1. The compounds of interest separated best on the μ-Bondapak phenyl column (Waters Associates) using 62:38 water/methanol with 0.004M sodium heptane sulfonate and 1% acetic acid. A typical sample and standard chromatogram are shown in Fig. 1 and 2, respectively. When a C-18 column was used, sodium benzoate coeluted with codeine.

Standard linearity was checked by assaying standards ranging from 25 to 200% of the target value. Relative standard deviation (2s%) for chromatographic variability was found to be 2.00 for guaifenesin, 2.63 for phenylpropanolamine hydrochloride, 1.66 for sodium benzoate, and

TABLE 1

Effect of Mobile Phase Composition & Column Polarity on Retention Time

No.	Solvent System	Flow Rate ml/min.	Column	Phenylpropanol-amine·HCl RT (min.)	Guaifenesin (RT (min.)	Phosphate RT (min.)	Benzoate RT (min.)
1	A + B 60: 40	1.0	C-18	11.7	7.3	9.5	9.5
2	A + B 60: 40	1.0	Phenyl	7.4	7.0	9.0	7.8
3	A + B 65: 35	1.0	Phenyl	10.1	9.0	13.5	11.0
4	A + B 65: 35	0.9	Phenyl	12.0	10.6	16.7	13.0
5	A + B 62: 38	0.5	Phenyl	16.76	15.02	20.35	18.30

A - 0.004M sodium heptane sulfonate in water with 1% glacial acetic acid.

B - 0.004M sodium heptane sulfonate in MeOH with 1% glacial acetic acid.

1.59 for codeine phosphate. Relative standard deviation (2s%) for procedural variability was found to be 2.89 for guaifenesin, 5.02 for phenylpropanolamine hydrochloride, 2.69 for sodium benzoate, and 1.86 for codeine phosphate.

Accuracy of the assay was determined by spiking and assaying sample preparations in duplicate. The spikes were done at 100% of the target value. Table 2 contains the % recoveries obtained for each spike and the average percent recoveries.

Specificity of the assay was shown by injecting the placebo containing dyes, flavors and excipients to determine if there was an interference. No interference was noted. The assay is stability-indicating. A

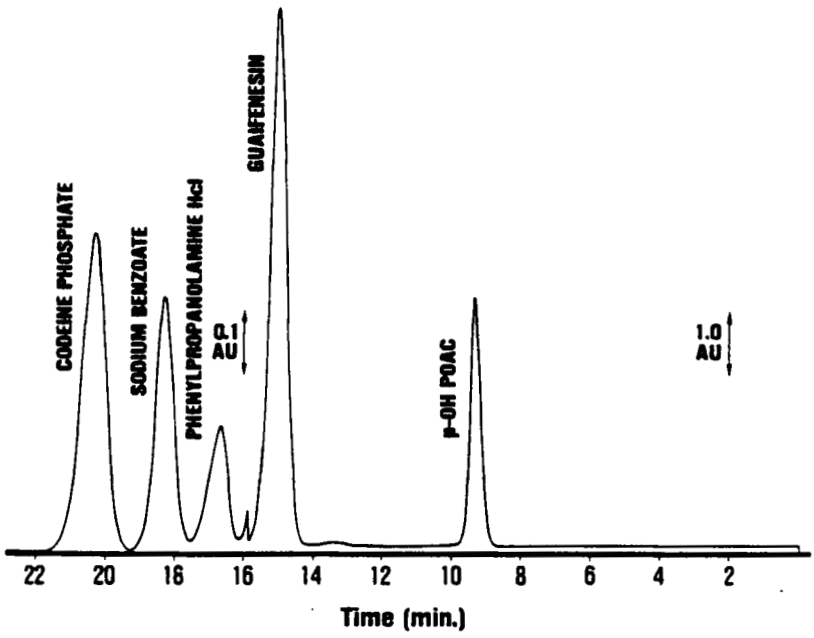

FIGURE 1

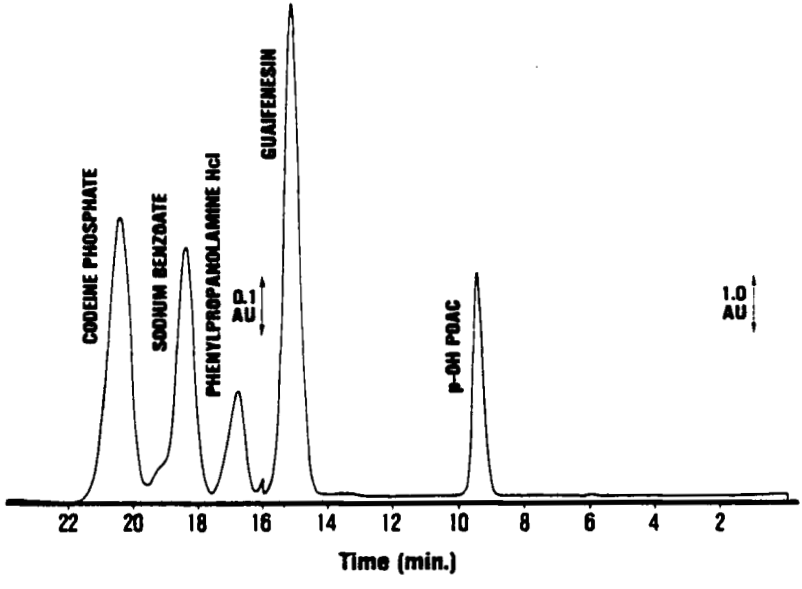

FIGURE 2

TABLE 2

Spike Recoveries

% Recoveries For:	Guaifenesin	Phenylpropanol-amine·HCl	Sodium Benzoate	Codeine Phosphate
	98.67 96.98	104.06 101.79	101.22 97.19	97.92 86.14
	$\bar{X}$ 97.83	$\bar{X}$ 102.63	$\bar{X}$ 99.21	$\bar{X}$ 92.02

syrup sample was placed in a temperature-controlled water bath at 60°C and aliquots were withdrawn and assayed at 24, 48, and 72 hours. Table 3 contains the initial % recovery, the assay variability range as determined by the overall assay precision, and the % recovery determined at each interval. During this stability study no interference was noted.

Several cough syrups were analyzed by the described method. The results are shown in Table 4.

TABLE 3

Stability Results

Active Ingredient	Initial % Recovery	Assay Variability Range	% Recovery		
			24 hrs.	48 hrs.	72 hrs.
Guaifenesin	97.83	100.65 - 95.00	93.5	98.26	93.91
Phenylpropanolamine HCl	102.63	107.78 - 97.48	96.7	106.8	96.5
Sodium Benzoate	99.21	101.88 - 96.54	100.0	100.5	99.5
Codeine Phosphate	92.02	93.73 - 90.31	93	101.78	101.53

TABLE 4

Assay Results on Various Ingredients

Using High-Pressure Liquid Chromatography

	% of Label Claim Found			
Syrup	Guaifenesin	Phenylpropanolamine HCl	Sodium Benzoate	Codeine Phosphate
1	100	94	106	102
2	102	99	106	100
3	98	101	117	102
4	95	92	106	95
5	96	96	100	95
6	95	98	110	100

In summary, a stability-indicating paired-ion HPLC assay method has been validated. The method does not require any fancy sample preparation. The accuracy and specificity of the method has been shown to be good.

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