Quantitative Gas Chromatographic Determination of Methapyrilene Fumarate, Ephedrine Hydrochloride, and Codeine Phosphate in Syrup

By HAROLD J. WESSELMAN and WILLIAM L. KOCH

A method for determining methapyrilene fumarate, ephedrine hydrochloride, and codeine phosphate simultaneously by gas chromatography is described. Temperature programming plus the use of an internal standard provide a simple and rapid method for separating and determining the three components in a syrup. Precision and accuracy studies are included.

BROCHMANN-HANSSEN AND Svendsen (1) determined ephedrine by gas chromatography in 1962. At about the same time Fales and Pisano (2) reported the determination of ephedrine as did Parker, Fontan, and Kirk (3). The latter authors (4) also determined codeine as did Massingill and Hodgkins (5) and Mule (6). Later Fontan, Smith, and Kirk (7) and Mac Donald and Pflaum (8) were able to determine methapyrilene. All of these determinations were qualitative in nature.

The quantitative determination of methapyrilene was performed by Celeste and Turczan (9) while the quantitative determination of codeine was done by Schmerzler *et al.* (10).

While the syrup can be assayed using an infrared or a combination spectrophotometric and titrimetric procedure, these methods leave much to be desired as several interdependent correction factors must be applied to the infrared and ultraviolet absorbance values obtained from tediously prepared extracts. In the present method, a simplified extraction procedure is combined with gas chromatography to give a rapid assay.

EXPERIMENTAL

Equipment—A linear programmed-temperature gas chromatograph (F and M Scientific Corp., model 402), equipped with a flame-ionization detector, was used for the experimental work. The detector signal was fed to a Honeywell Electronic 16 1-mv. recorder with a chart speed of 15 in./hr. and a 1-sec. full scale response. Samples were injected with a 10-μl. Hamilton, No. 701, syringe.

Materials—Helium was used as a carrier gas, while electrolytic hydrogen and oxygen were used in the detector. The stationary phase was 3.8% Linde W-98 silicone gum applied by the solution technique of Horning *et al.* (11) to Diatoport S (80–100 mesh) and packed in dual borosilicate glass columns (91 cm. × 6.4 mm.). Chloroform (analytical reagent grade) was used to dissolve the free bases obtained from the commercially available methapyrilene fumarate, ephedrine hydrochloride, and codeine phosphate.

Operating Conditions—The column temperature was programmed from 145–255° at a heating rate of 10° per min. At the end of each programmed run, the column oven was cooled for exactly 10 min. and then equilibrated for exactly 10 min. at 145° before injecting the next sample. These times were selected to keep the assay within practical limits of time and precision. The helium flow rate was 55 ml. per min. with an inlet pressure of 40 psig. Oxygen and hydrogen flow rates were 300 and 35 ml./min., respectively. The sample injection port and the detector block were maintained at 285°. One-microliter injections of all samples were used throughout. The electrometer range was 10 with an attenuation of 256.

Quantitative Analysis—The internal standard technique of Ray (12) was used because of its accuracy. In this method amobarbital is employed as the internal standard.

A 10.0-ml. sample of the syrup is placed into a 125-ml. separator containing 15 ml. water. Then add 1.5 ml. 1:1 sodium hydroxide to make the mixture basic. Extract the mixture with four 25-ml. portions of chloroform and filter the extracts through anhydrous sodium sulfate into a 150-ml. beaker. Using a stream of dry air and a water bath, evaporate the chloroform to a volume of about 3 ml. Transfer quantitatively the extracts to a 10-ml. volumetric flask, add exactly 2.0 ml. of chloroform containing 20.0 mg. amobarbital, and dilute to volume with chloroform. In a like manner prepare a standard solution by extracting 20.0 mg. codeine phosphate, 10.0 mg. ephedrine hydrochloride, and 27.0 mg. methapyrilene fumarate dissolved in 25.0 ml. water.

Chromatograph the standard and the sample solutions and measure the peak heights of each com-

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ponent. Calculate the amounts of each component in the syrup by using the following formulas:

$$\frac{\text{standard amobarbital peak height/standard ephedrine peak height}}{\text{sample amobarbital peak height/sample ephedrine peak height}} \times 1.0 = \text{mg. ephedrine hydrochloride/ml. syrup}$$

$$\frac{\text{standard amobarbital peak height/standard methapyrilene peak height}}{\text{sample amobarbital peak height/sample methapyrilene peak height}} \times 2.7 = \text{mg. methapyrilene fumarate/ml. syrup}$$

$$\frac{\text{standard amobarbital peak height/standard codeine peak height}}{\text{sample amobarbital peak height/sample codeine peak height}} \times 2.0 = \text{mg. codeine phosphate/ml. syrup}$$

PRECISION AND ACCURACY

To determine the precision and accuracy of the method, a freshly prepared solution of the three components in distilled water was used as the standard solution. This solution was chromatographed five times and the peak height ratios for each component were averaged to obtain values which were then used in the calculations for the sample solution. The relative standard deviations for ephedrine, methapyrilene, and codeine are ±3.76, ±2.38, and ±2.02%, respectively. Since the ratios for the standard solution are fairly constant and reproducible, this solution need be chromatographed only two times when routine assays are performed. The sample solution was prepared by dissolving the same three components in a freshly made syrup blank. These studies were carried out in accordance with the suggestions of the Advisory Board of Analytical Chemistry (13) and the recommended nomenclature is used. Table I shows the results of these studies.

The precision of the method was also examined by having another analyst assay a production lot of the syrup. Each of five replicate extractions was chromatographed five times. The relative standard deviation values could probably be improved if a longer equilibration period is allowed before beginning the programmed temperature run. The results of this study are recorded in Table II.

Table I—Precision and Accuracy Study

	Ephedrine	Methapyrilene	Codeine
	Standard Solution, mg./ml.		
	1.00	2.70	2.00
	Sample Solution, mg./ml.		
$\bar{X}$	1.01	2.71	1.99
N	25	25	25
s	0.0669	0.0946	0.0425
RSD	±6.62%	±3.49%	±2.14%
Mean error	+0.01	+0.01	−0.01
Relative error	+1.00%	+0.37%	−0.50%

Table II—Precision Study of a Production Lot of Syrup of Methapyrilene Fumarate, Ephedrine Hydrochloride, and Codeine Phosphate

	Ephedrine Hydrochloride	Methapyrilene Fumarate	Codeine Phosphate
Theory, mg./ml.	1.00	2.90	2.00
N	25	25	25
$\bar{X}$	1.00	3.08	2.11
RSD	±7.76%	±4.78%	±4.93%

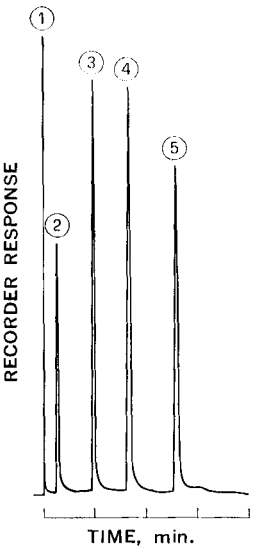

Fig. 1—Typical gas chromatogram for chloroform (1), ephedrine (2), amobarbital (3), methapyrilene (4), and codeine (5).

Table III—Analysis of Syrup of Methapyrilene Fumarate, Ephedrine Hydrochloride, and Codeine Phosphate

	Ephedrine Hydrochloride	Methapyrilene Fumarate	Codeine Phosphate
Theory mg./ml.	1.00	2.90	2.00
Lot No.			
A[a]	1.01	2.93	1.98
B[b]	1.05	2.85	2.05
C[b]	1.01	2.82	2.00
D[c]	1.01	2.92	2.00
E[c]	1.01	2.94	2.00

[a] Average of 10 determinations; RSD values similar to those of Table II. [b] Average of 5 determinations. [c] Average of 3 determinations.

The results indicate that while the precision is less than anticipated, it is better than conventional methods which are combinations of spectrophotometric and titrimetric procedures. This method has the important advantage of being specific for each component. Efforts are being made to increase the precision of the method by improving the temperature programming technique.

RESULTS AND DISCUSSION

A typical chromatogram of a mixture of methapyrilene, ephedrine, codeine, and amobarbital is shown in Fig. 1. Table III shows the results of the assay of five production lots of the syrup. The overall time for determining the standard and the sample amounts to approximately 1.5 hr.

CONCLUSION

A simplified method for determining methapyrilene fumarate, ephedrine hydrochloride, and codeine phosphate by means of gas chromatography is presented. The use of temperature programming plus an internal standard result in a good separation

of the three components which have widely spaced boiling points.

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Keyphrases

Methapyrilene fumarate, ephedrine HCl, codeine PO_4 syrup—analysis
Simultaneous determination
GLC—analysis
Amobarbital—internal standard

Quantitative Determination of Some Single and Multiple Component Drugs by Gas-Liquid Chromatography

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A gas-liquid chromatographic procedure has been developed to separate and quantitate various drug mixtures. The samples are extracted by various techniques and determined by the use of a polar (4 percent cyclohexanedimethanol succinate) or a polar–nonpolar (1 percent cyclohexanedimethanol succinate plus 10 percent SE 52 silicone gum rubber) gas-liquid column. Retention data relative to pentobarbital are presented for 50 drug materials. Quantitative data are presented for 25 different drugs found in 19 commercial preparations, and for 7 synthetically prepared drug combinations. Recoveries ranged from 96 to 106 percent.

GAS-LIQUID CHROMATOGRAPHY (GLC) has been used to successfully separate antihistamines (1–5), barbiturates (6–11), and alkaloids (12–14) where several of the same class occur together. Many multiple component drugs, however, are not confined to a single class of ingredient (*e.g.*, barbiturates only) but have a variety of active ingredients. The purpose of this study was to find appropriate column materials for GLC which could be used to separate various classes of drugs in a single dosage form.

Previous reports on drug separation by GLC (2, 5, 11, 12) indicate that columns containing either polar or polar–nonpolar liquid phases give more symmetrical peaks for a larger number of drugs than nonpolar liquid phases. Peak symmetry is desirable for accurate quantitation of drugs. Two such columns were investigated in this study.

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Nineteen commercial drug preparations were analyzed. These drugs were in several dosage forms including tablets, capsules, liquids, and lotions. They contained from one to ten active ingredients each, but a maximum of six ingredients was analyzed in any one sample.

Seven synthetic drug mixtures were also analyzed. These mixtures were prepared, in most cases, with the concentration of active ingredients and excipients (starch, lactose, and magnesium stearate) equivalent to commercial drug preparations.

EXPERIMENTAL

Column Preparation

A mixed column of 1% HI-EFF-8BP (cyclohexanedimethanol succinate) + 10% SE 52 (a methylphenyl silicone gum rubber) on Gas Chrom Q (Column A) and a polar column of 4% HI-EFF-8BP on Gas Chrom Q (Column B) were prepared and conditioned in the following manner.

Column A—Into a 600-ml. beaker, 200 mg. of HI-EFF-8BP (Applied Science Laboratories) and