Simultaneous Determination of Nonderivatized Phenylpropanolamine, Glyceryl Guaiacolate, Chlorpheniramine, and Dextromethorphan by Gas Chromatography

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Abstract □ A gas chromatographic procedure is described for the rapid and quantitative determination of phenylpropanolamine, glyceryl guaiacolate, chlorpheniramine, and dextromethorphan in a commercially available cough-cold preparation. Pramoxine is used as the internal standard. The active ingredients are extracted in chloroform and injected without further treatment. A single chromatogram, obtained isothermally, quantitatively resolves all four ingredients.

Keyphrases □ Phenylpropanolamine, glyceryl guaiacolate, chlorpheniramine, dextromethorphan—simultaneous determination □ GLC—analysis □ Pramoxine—GLC internal standard

In recent years, the introduction of cough-cold preparations containing several active ingredients has increased sharply. The combining of antitussive, antipyretic, and antihistaminic drugs has distinct commercial advantages in that several cough-cold symptoms can be treated simultaneously with a single preparation. However, these combination-dose forms present serious difficulties to the quality control analyst who is concerned with identification and independent quantitation of each active ingredient. Classical wet methods are time consuming, expensive, and frequently of little use when the physical-chemical properties of two or more ingredients are relatively similar. The applicability of gas chromatography to pharmaceutical analysis is well documented in the literature (1–10), and the resolution of many types of mixtures has been published. Serious difficulties are often encountered when relatively polar compounds of high molecular weight are chromatographed (11). These materials often exhibit excessive tailing, and the selection of the liquid phase becomes very critical if resolution is to be obtained. The problem is compounded when active ingredients of widely divergent polarities are present in a given mixture. In a recent article, Hishta and Laubach (12) analyzed a mixture of phenylpropanolamine, phenylephrine, phenyltoloxamine, and chlorpheniramine by gas chromatography after forming the bistrimethylsilylacetamide (BSA) derivative.

This investigation was undertaken to study the advisability of using a low liquid load of nonpolar silicon rubber SE-30 in a modified all-glass system for the resolution of a multicomponent drug mixture containing ingredients of widely divergent polarities without the use of derivatives. In initial studies utilizing metal columns, it was found that the results were often inconsistent, showing incomplete recovery and excessive peak tailing. Apparently the active ingredients, when present in the free base form, interact in some way with metal surfaces. On modification to an all-glass, on-column injection system, these problems were eliminated.

EXPERIMENTAL

Equipment—A Varian Aerograph model 1200-1 with flame ionization detector was used for the experimental work. The column used was a 2.44-m. (8-ft.) coiled Pyrex glass, 0.32-cm. (0.125-in.) o.d., packed with 2% SE-30 on 80/100-mesh diatomite [Chromosorb W (HP), acid washed and silanized]. Gas flow rates of 30 ml./min. for hydrogen, 30 ml./min. for helium, and 300 ml./min. for air were used. The instrument was modified by replacing the 0.64-cm. (0.25-in.) injection port containing 0.32-cm. (0.125 in.) metal inserts with an 0.32-cm. (0.125-in.) injection port, and the column was extended through the port to the septum. Injection was on-column, and therefore the sample did not come in contact with any metal surface except for the brief instant it passed through the syringe needle during injection. The detector oven and injection port were maintained at 270°. The column oven temperature was held isothermal at 180° through the analysis.

Reagents—The pramoxine internal standard was prepared by weighing approximately 1 g. of pramoxine hydrochloride of known purity into a 250-ml. separator containing 25 ml. of deionized water. After solution was effected, 25 ml. of 50% sodium hydroxide solution was added cautiously to the aqueous phase in the separator while cooling under cold tap water. This solution was then extracted with four 20-ml. portions of chloroform. The chloroform extracts were filtered through cotton and pooled in a 100-ml. volumetric flask. The total volume was adjusted to 100 ml. with chloroform. The solution, when refrigerated, was stable for approximately 6 weeks.

Sample Preparation—A commercially available cough-cold preparation was analyzed in this study.[1] The sample was prepared by pipeting 25.0 ml. of the "cough syrup" into a 250-ml. separator. Five milliliters of concentrated hydrochloric acid was added and the sample extracted with three 30-ml. portions of carbon tetrachloride. The carbon tetrachloride extracts were pooled and backwashed once with 30 ml. of deionized water. The aqueous extracts were pooled in a 250-ml. separator and the carbon tetrachloride phase discarded. Twenty-five milliliters of 50% sodium hydroxide was then added cautiously to the aqueous phase and cooled periodically under cold tap water. The sample was then extracted with seven 30-ml. portions of chloroform, adding 5 g. of sodium chloride to the combined phases during each of the first four extracts. The chloroform extracts were filtered through cotton and pooled in a 250-ml. wide-mouth beaker. The extracts were evaporated continuously (*but never to dryness*) on a steam bath with a stream of forced air. Evaporation was continued until approximately 25 ml. of the combined chloroform extracts remained. This volume was transferred quantitatively to a 50-ml. volumetric flask to which 5.0 ml. of the pramoxine internal standard reagent had been added. The total volume was adjusted to 50 ml. with chloroform.

Standard Preparation—A standard was prepared by weighing to the nearest tenth of a milligram approximately 55 mg. of phenylpropanolamine hydrochloride, 75 mg. of glyceryl guaiacolate, 5 mg. of chlorpheniramine maleate (prepared by weighing and dissolving 100 mg. of chlorpheniramine maleate into 100.0 ml. of deionized water and pipeting 5 ml. of this stock solution), and 37.5 mg. of dextro-

[1] Coldene Cough and Cold, trade name of Pharmacraft Division, Pennwalt Corp., Rochester, NY 14623

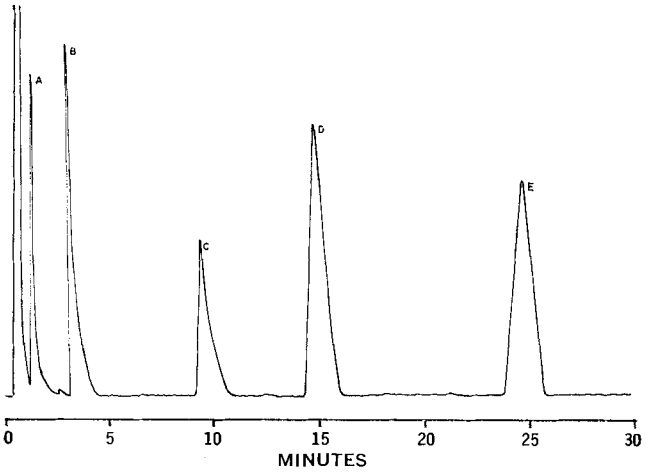

Figure 1—*Typical chromatogram. Key: A, phenylpropanolamine; B, glyceryl guaiacolate; C, chlorpheniramine; D, dextromethorphan; and E, pramoxine.*

methorphan hydrobromide into a 250-ml. separator containing approximately 25 ml. of deionized water. After solution was effected, this standard solution was treated exactly as described for the sample solution, including the addition of 5.0 ml. of pramoxine.

Procedure and Analysis—A 10-μl. Hamilton syringe equipped with a Chaney adapter was used to inject 2.0 μl. of the sample and standard solutions alternately. Values were calculated by peak height measurement. Since a completely synthetic standard was prepared in a manner identical to the procedure used to obtain the sample, and the detector response was linear within concentrations of ±25% of theory (see *Results and Discussion*), the ratio of the peak heights in the internal standard to each unknown could be stated in constant proportion to the ratio of their amounts, that is

$$\left[\frac{H_x}{H_s}\right]_\alpha = \left[\frac{C_x}{C_s}\right]_\alpha \qquad \text{(Eq. 1)}$$

and

$$\left[\frac{H_x}{H_s}\right]_\beta = \left[\frac{C_x}{C_s}\right]_\beta \qquad \text{(Eq. 2)}$$

where H_x is the peak height of the individual component to be analyzed, H_s is the peak height of the pramoxine internal standard, C_x is the concentration of the component in mg./ml., C_s is the concentration of the pramoxine internal standard in mg./ml., α is the ratio within the standard solution, and β is the ratio within the sample solution. Combining Eqs. 1 and 2,

$$\left[\frac{H_x}{H_s}\right]_\alpha \left[\frac{C_x}{C_s}\right]_\beta = \left[\frac{H_x}{H_s}\right]_\beta \left[\frac{C_x}{C_s}\right]_\alpha \qquad \text{(Eq. 3)}$$

Rearranging Eq. 3,

$$\left[\frac{C_x}{C_s}\right]_\beta = \frac{\left[\frac{H_x}{H_s}\right]_\beta \left[\frac{C_x}{C_s}\right]_\alpha}{\left[\frac{H_x}{H_s}\right]_\alpha} \qquad \text{(Eq. 4)}$$

But the concentration of the internal standard is held constant in both the sample (β) and the standard (α) solutions. Therefore, Eq. 4 simplifies to

$$[C_x]_\beta = \frac{\left[\frac{H_x}{H_s}\right]_\beta [C_x]_\alpha}{\left[\frac{H_x}{H_s}\right]_\alpha} \qquad \text{(Eq. 5)}$$

Since the term $[C_x]_\alpha$ is known, and $[H_x/H_s]_\alpha$ and $[H_x/H_s]_\beta$ are measured experimentally, Eq. 5 can be solved for $[C_x]_\beta$ (the mg./ml. of unknown in sample). The values obtained from Eq. 5 were compared to the theoretical amounts of each component and the percent recovered calculated.

Table I—Evaluation of the Linearity of Detector Response in Samples Containing 75 and 125% of Theoretical Drug Quantities

Ingredient	Theoretical, mg./5 ml.	Found, mg./5 ml.	% Theory Recovered
Phenylpropanolamine	8.25	8.44	102.30
	13.75	13.94	101.38
Glyceryl guaiacolate	11.25	11.06	98.31
	18.75	18.93	100.96
Chlorpheniramine	0.75	0.74	98.66
	1.25	1.25	100.00
Dextromethorphan	5.63	5.72	101.60
	9.38	9.33	99.47

RESULTS AND DISCUSSION

A typical chromatogram is shown in Fig. 1. All the peaks are symmetrical and well resolved. Table I contains data of the detector response in a concentration range of ±25% of the theoretical drug quantities contained in the sample preparation. Table II contains the recovery data for the four active ingredients in duplicate samples of 10 different lots of the cough preparation calculated from peak height values. Precision and accuracy data are also presented and indicate excellent reproducibility.

The initial preextraction of the cough preparation with carbon tetrachloride was necessary to remove the organic soluble flavor and coloring additives which interfere with the chromatogram.

A simplified single-injection, gas chromatographic method for determining phenylpropanolamine, glyceryl guaiacolate, chlorpheniramine, and dextromethorphan in a commercially available cough preparation has been presented. The use of an isothermal method results in excellent resolution of all four components not withstanding their widely divergent polarities and boiling points. The modification of the chromatograph to an all-glass, on-column injection system yields quantitative, reproducible results. The pro-

Table II—Experimental *versus* Theoretical Quantities of Drug Actives Calculated from Peak Height Data

	mg./5 ml.			
	Phenyl-propanol-amine	Glyceryl Guaiaco-late	Chlor-phen-iramine	Dextro-methor-phan
Theoretical quantity	11.0	15.0	1.00	7.5
Lot A (1)	11.0	14.6	0.98	7.4
(2)	11.2	15.0	1.02	7.6
Lot B (1)	11.1	15.2	1.00	8.0
(2)	10.6	14.6	1.01	7.8
Lot C (1)	11.0	15.6	1.04	7.2
(2)	11.0	15.0	1.01	7.4
Lot D (1)	10.7	15.9	1.02	7.8
(2)	10.7	15.5	1.04	7.6
Lot E (1)	11.1	15.3	1.05	7.4
(2)	11.0	15.5	1.03	7.2
Lot F (1)	11.2	15.6	1.01	7.5
(2)	10.5	14.6	0.96	7.3
Lot G (1)	11.0	14.7	0.97	7.2
(2)	11.0	15.3	0.97	7.4
Lot H (1)	10.8	15.4	1.02	7.4
(2)	10.8	15.2	0.99	7.6
Lot I (1)	11.1	15.7	1.04	7.4
(2)	11.0	15.6	1.03	7.7
Lot J (1)	10.0	15.0	0.99	7.4
(2)	10.6	14.9	0.98	7.4
Average	10.9	15.2	1.01	7.5
Relative *SD* of preparation, %	1.99	2.55	2.51	2.74
Relative *SD* of preparation from label claim, %	2.28	2.98	2.79	2.74

cedure described in this paper is being applied to a series of complex pharmaceutical mixtures which will be the subjects of future articles.

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TECHNICAL ARTICLES

Utilization of the Solids Processor for Preparation of Tablet Granulations

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Abstract □ Various factors relating to the use of vacuum tumble dryers for the preparation of tablet granulations were studied. A dryer was employed (the 1-cu. ft. solids processor) which has a working capacity of 15–18 kg. for most pharmaceutical granulations. A typical process involves the wetting of the substrate with a drug solution and then drying at a predetermined temperature and vacuum. It was found that uniform drug distribution for low-dose tablet formulations could be obtained. Drying rates were determined for spray-dried lactose and dicalcium phosphate dihydrate at two temperatures and three tumbling speeds. Drying times varied from 35 to 60 min. A series of modified direct compression formulations was studied in which microcrystalline cellulose was used at two levels; two lubricants, calcium stearate and stearic acid, were employed; and lubricant addition was carried out by two methods, internal and external. The effects of these factors on tableting characteristics were monitored by an instrumented tablet machine (Stokes BB-2), and the final physical properties of the tablets were determined. A series of antacid granulations was prepared in which the influence of mixing time and the amount of granulating fluid was varied. The resulting granulations and tablets were characterized as described above.

Keyphrases □ Solids processor—preparation, tablet granulations □ Tablet granulations, preparation—solids processor □ Vacuum tumble dryers—data, mixing, drying, formulation, processing factors

New technology for the formulation of solid dosage forms has been developed over the past 5–10 years. The availability of new materials *per se*, new forms of old materials, and the invention and utilization of new machinery have allowed the formulation and manufacture of many products by simplified methods. Thus, the use of direct compression of medicinals, especially those in the low- and medium-dose range, has overtaken older traditional methods of wet granulation and slugging. Emphasis on faster dissolution rate and providing the drug in a readily available form are other reasons for updating tablet formulation and technology.

Some methods for simplified processing of tablet granulations have been described. A spray-drying process was reported by Raff *et al.* (1). A placebo granulation was prepared by spray drying and the drug, colorant, and tablet lubricant were added to the granulation and blended. A one-step spray-drying process could conceivably be feasible if the high inlet temperature would not physically or chemically affect the drug. Later, Kornblum described a spray-drying process for the preparation of a granulation for the formulation of sustained-action tablets (2).

The Littleford-Lodge mixer has been shown to be of value in mixing small quantities of active ingredients with inert diluents (3). In experiments using 250 mcg. of micronized salicylamide per 100 mg. of terra alba, coefficients of variation for drug content were from about 1 to 4% over a 0.5–10-min. interval of mixing. Mixing unmicronized salicylamide gave a significantly higher coefficient of variation.

An air-suspension technique for the preparation of tablet granulations was described by Wurster (4). These granulations were 16–20% active by weight, and deviation of content from theory was about −1 to +6%. The amount of solids lost was 1–8%.

Some of these methods might be satisfactory for active products in the low-dose range, arbitrarily in the