Automated, Simultaneous Determination of Dextromethorphan Hydrobromide, Glyceryl Guaiacolate, and Phenylpropanolamine Hydrochloride in Cough Syrups

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Abstract ☐ An automated analytical method for the simultaneous colorimetric determination of dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride in cough syrups was developed. The method significantly reduced the analysis time to 0.4 hr./sample and the relative standard deviations obtained were 1.36, 1.16, and 0.79%, respectively.

Keyphrases ☐ Dextromethorphan hydrobromide mixtures with glyceryl guaiacolate and phenylpropanolamine hydrochloride—automated, simultaneous colorimetric analysis ☐ Glyceryl guaiacolate mixtures with dextromethorphan hydrobromide and phenylpropanolamine hydrochloride—automated, simultaneous colorimetric analysis ☐ Phenylpropanolamine hydrochloride mixtures with dextromethorphan hydrobromide and glyceryl guaiacolate—automated, simultaneous colorimetric analysis ☐ Cough syrups—simultaneous analysis of dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride ☐ Colorimetry -analysis, dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride mixtures

With the wide use of an effective antitussive combined with an expectorant and a bronchodilator in cough syrups, the need for a rapid simultaneous method of analysis existed for the determination of dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride. Several investigators reported on the simultaneous analysis of cough–cold preparations using GLC. Mario and Meehan (1) determined the three respective components and chlorpheniramine, Rader and Aranda (2) determined 50 compounds including the three components, and Goebbeler (3) determined dextromethorphan hydrobromide and phenylpropanolamine hydrochloride along with chlorpheniramine and salicylamide. However, the reported methods require manual sample preparation, *i.e.*, direct dilution, liquid–liquid extraction, or liquid–liquid partition chromatography, prior to injection of the sample into the gas chromatograph. An automated procedure[1] was developed by Ek *et al.* (4) for the simultaneous determination of total antihistamines by UV spectrophotometry, individual antihistamines by GC, and phenylpropanolamine hydrochloride by colorimetry using the dimethoxytetrahydrofuran reaction.

Although a wide variety of multicomponent pharmaceutical preparations have been analyzed using simultaneous automated procedures (5–7), the specific analysis of the three commonly used components in cough syrups has not been performed simultaneously using an automated system. This paper describes the simultaneous automated determination of the three active components, with initial sample dilution as the only manual step. Dextromethorphan hydrobromide is determined *via* ion-pair formation with bromcresol green, glyceryl guaiacolate is determined *via* reaction with formaldehyde in sulfuric acid–methanol, and phenylpropanolamine hydrochloride is determined *via* the ninhydrin reaction.

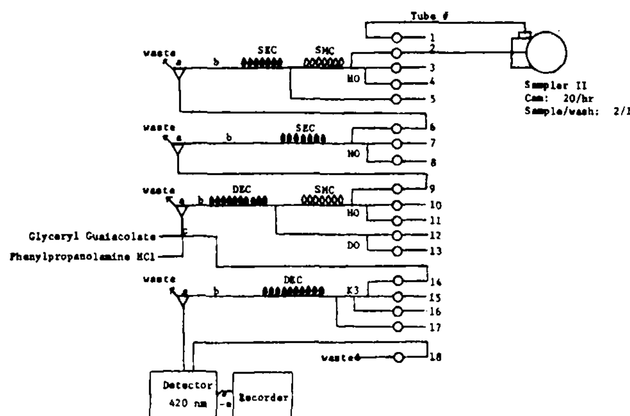

Figure 1—*Flow diagram for sample cleanup, extraction, and dextromethorphan hydrobromide determination. Key: 1, 2.50 ml./min. water (Standard); 2, 2.00 ml./min. sample (Standard); 3, 1.20 ml./min. 1 N hydrochloric acid (Standard); 4, 0.6 ml./min. air (Standard); 5, 2.42 ml./min. petroleum ether (Solvaflex); 6, 2.00 ml./min. sample (Standard); 7, 2.42 ml./min. petroleum ether (Solvaflex); 8, 0.60 ml./min. air (Standard); 9, 1.60 ml./min. sample (Standard); 10, 1.20 ml./min. 1 N sodium hydroxide (Standard); 11, 0.60 ml./min. air (Standard); 12, 13, 2.03 ml./min. chloroform (Acidflex); 14, 1.19 ml./min. sample (Acidflex); 15, 1.71 ml./min. chloroform (Acidflex); 16, 0.60 ml./min. air (Standard); 17, 2.50 ml./min. bromcresol green–buffer solution (Standard); 18, 2.03 ml./min. cell return (Acidflex); SMC, 14-turn mixing coil; SEC, 14-turn beaded coil; DEC, 28-turn beaded coil; a, B-0 separator; b, 15.2-cm. (6-in.) 0.110-i.d. Teflon tubing; and c, G-3 connector.*

EXPERIMENTAL

Reagents—The following reagents were used: 1 *N* hydrochloric acid, 1 *N* sodium hydroxide, petroleum ether[2] (low boiling, 30–60°), and chloroform[3].

pH 5.3 Buffer—Dissolve 38 g. of monobasic sodium phosphate[4], $NaH_2PO_4 \cdot H_2O$, and 3.8 g. of dibasic sodium phosphate[4], $Na_2HPO_4 \cdot 7H_2O$, in sufficient water to make 1 l. of solution. Check the pH and adjust if necessary.

Bromcresol Green–Buffer Solution—Dissolve 0.10 g. of tetrabromo-*m*-cresolsulfonphthalein sodium salt[5] in 1 l. of pH 5.3 buffer. Filter prior to use.

Sulfuric Acid–Methanol–Water Solution (60:20:20)—Cautiously mix 600 ml. of concentrated sulfuric acid with 200 ml. of methanol and 200 ml. of water in an ice bath.

Formaldehyde–Methanol Solution—Dilute 30 ml. of 38% form-

[1] Using the AutoAnalyzer, Technicon Instruments Corp., Tarrytown, N. Y.

[2] J. T. Baker Chemical Co.
[3] Certified ACS, Fisher Scientific Co.
[4] Mallinckrodt Chemical Works.
[5] Allied Chemical Corp.

Table I—Determination of Dextromethorphan Hydrobromide, Glyceryl Guaiacolate, and Phenylpropanolamine Hydrochloride in Cough Syrups

Sample	Components	Label Claim, mg./5 ml.	Manual Assay[a], mg./5 ml.	Automated Assay, mg./5 ml.		
				Range	Average	*RSD*
A	Dextromethorphan hydrobromide	15.0	15.2	15.0–15.3	15.2[b]	0.47
	Glyceryl guaiacolate	100.0	100.5	99.6–101.5	100.8[b]	0.76
B	Dextromethorphan hydrobromide	7.5	7.47	7.64–7.74	7.70[c]	0.58
	Glyceryl guaiacolate	25.0	24.3	25.6–26.1	25.9[c]	0.72
C	Dextromethorphan hydrobromide	7.5	7.56	7.44–7.64	7.54[b]	0.84
	Glyceryl guaiacolate	37.5	37.8	37.7–38.1	38.0[b]	0.83
	Phenylpropanolamine hydrochloride	8.75	8.83	8.72–8.85	8.79[b]	0.51
D	Dextromethorphan hydrobromide	5.0	5.05	5.14–5.20	5.17[c]	0.46
	Glyceryl guaiacolate	50.0	50.4	50.1–51.3	50.6[c]	0.92
	Phenylpropanolamine hydrochloride	12.5	13.4	13.1–13.2	13.1[d]	0.34

[a] Average of two manual determinations. [b] Average of 10 determinations. [c] Average of five determinations. [d] Average of four determinations.

aldehyde solution[2] to 1 l. with absolute methanol.

pH 5 Citrate Buffer—Weigh 84.0 g. of citric acid monohydrate[6] into a 2-l. volumetric flask. Dissolve in 1 l. of water, add 32 g. of sodium hydroxide pellets[6], dissolve, and dilute to volume with water. Check the pH and adjust if necessary.

Ninhydrin Reagent—Dissolve 0.0261 g. of potassium cyanide[4] in 40 ml. of water and dilute to 1 l. with 2-methoxyethanol[7] (Solution I). Dissolve 10 g. of 1,2,3-indantrione monohydrate[7] in 200 ml. of 2-methoxyethanol (Solution II). Mix the total contents of both solutions and allow the reagent to stand overnight prior to use.

Apparatus—The automated system consisted of the following modules: Liquid Sampler II[8]; two Model III proportioning pumps[8]; two variable temperature heating baths[8], each equipped with two 2.4-mm. i.d. × 12.2-m. (40-ft.) coils[8]; three spectrophotometers[9]; and three recorders[10].

Procedure—*Standard Preparation*—Prepare accurately a standard solution in water containing 0.10–0.15 mg./ml. of dextromethorphan hydrobromide, 0.50–1.0 mg./ml. of glyceryl guaiacolate, and 0.15–0.26 mg./ml. of phenylpropanolamine hydrochloride.

Sample Preparation—Dilute accurately an aliquot of the cough syrup containing 10–15 mg. of dextromethorphan hydrobromide, 50–100 mg. of glyceryl guaiacolate, and 15–26 mg. of phenylpropanolamine hydrochloride to 100 ml. with water.

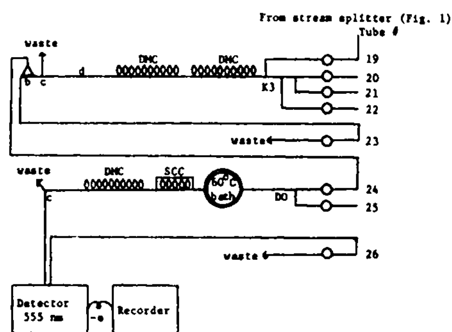

Figure 2—*Flow diagram for glyceryl guaiacolate determination. Key: 19, 1.19 ml./min. sample (Acidflex); 20, 2.03 ml./min. sulfuric acid–water–methanol reagent (Acidflex); 21, 0.6 ml./min. air (Standard); 22, 0.56 ml./min. formaldehyde–methanol reagent (Solvaflex); 23, 1.44 ml./min. waste (Acidflex); 24, 1.71 ml./min. sample (Acidflex); 25, 0.42 ml./min. air (Standard); 26, 1.19 ml./min. cell return (Acidflex); DMC, 28-turn coil; SCC, 14-turn jacketed cooling coil; a, C-1; b, B-0; c, C-3; and d, 15.2-cm. (6-in.) 0.110-i.d. Teflon tubing.*

[6] Fisher Scientific Co.
[7] Matheson, Coleman and Bell.
[8] Technicon Instruments Corp., Tarrytown, N. Y.
[9] Hitachi-Perkin-Elmer model III, Coleman Instruments.
[10] Model SRL, E. H. Sargent and Co.

Sample Testing—Place portions of the samples and standards into the 8.5-ml. polystyrene Liquid Sampler II cups. Place the samples in the odd-numbered spaces in the Liquid Sampler II turntable, interspersing the standards at periodic intervals. Into the even-numbered spaces, place cups containing water. The simultaneous automated analysis is then performed using the schematic flow diagrams shown in Figs. 1–3. Record the absorbances of the samples and standards at 420 nm. for dextromethorphan hydrobromide, at 555 nm. for glyceryl guaiacolate, and at 570 nm. for phenylpropanolamine hydrochloride.

RESULTS

The precision and accuracy for the measurement of each of the components were established by analyzing individual standard aliquots and four marketed cough syrups. For a minimum of 20 determinations, the relative standard deviations for dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride were 1.36, 1.16, and 0.79% at a concentration of 0.10, 1.00, and 0.25 mg./ml., respectively. Plots of the absorbance *versus* concentration for aliquots of dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride are presented in Fig. 4.

Samples of the four marketed cough syrups were analyzed using the automated colorimetric methods. The results obtained for dextromethorphan hydrobromide and glyceryl guaiacolate in cough syrups, Samples A–D, and phenylpropanolamine hydrochloride in cough syrups, Samples C and D, along with the labeled components and manual assay values, are presented in Table I.

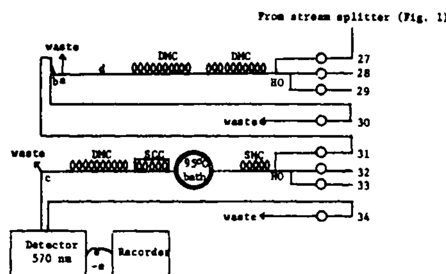

Figure 3—*Flow diagram for phenylpropanolamine hydrochloride determination. Key: 27, 1.19 ml./min. sample (Acidflex); 28, 2.50 ml./min. pH 5 citrate buffer (Standard); 29, 0.60 ml./min. air (Standard); 30, 1.44 ml./min. waste (Acidflex); 31, 2.03 ml./min. sample (Acidflex); 32, 1.44 ml./min. ninhydrin reagent (Acidflex); 33, 0.60 ml./min. air (Standard); 34, 2.42 ml./min. cell return (Solvaflex); DMC, 28-turn coil; SMC, 14-turn coil; SCC, 14-turn jacketed cooling coil; a, C-1; b, C-0; c, C-3; and d, 15.2-cm. (6-in.) 0.110-i.d. Teflon tubing.*

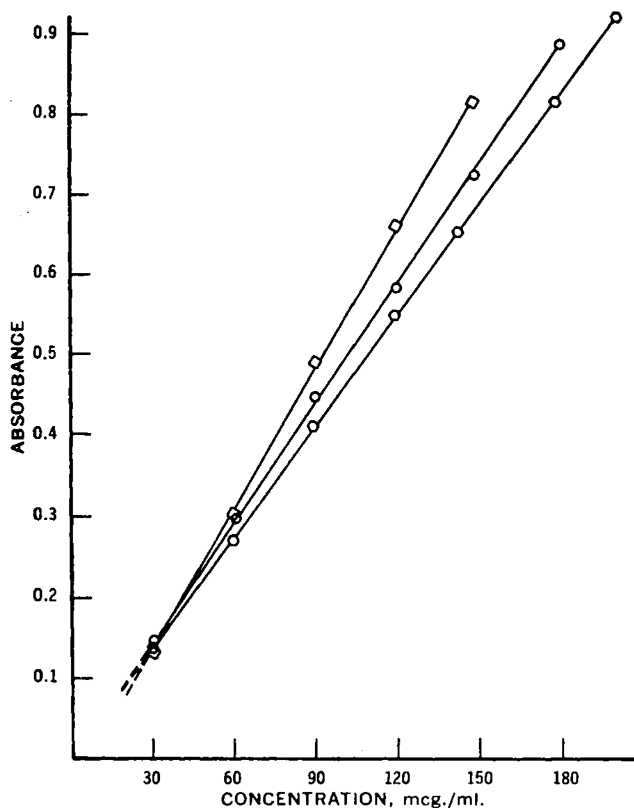

Figure 4—*Standard curves for dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride. Key:* O, *dextromethorphan hydrobromide (micrograms per milliliter);* □, *glyceryl guaiacolate (micrograms per milliliter × 6.67); and* O, *phenylpropanolamine hydrochloride (micrograms per milliliter × 1.67).*

Portions of the scans obtained for the sample analysis including standards are presented in Figs. 5–7.

DISCUSSION

The automated system was designed specifically for cough syrups containing only the following active components: dextromethorphan hydrobromide, glyceryl guaiacolate, and phenylpropanolamine hydrochloride. The system can be employed for the simultaneous determination of all three or any two components as well as the individual determination of any single component. The combined analytical methodologies cannot be completely applied to

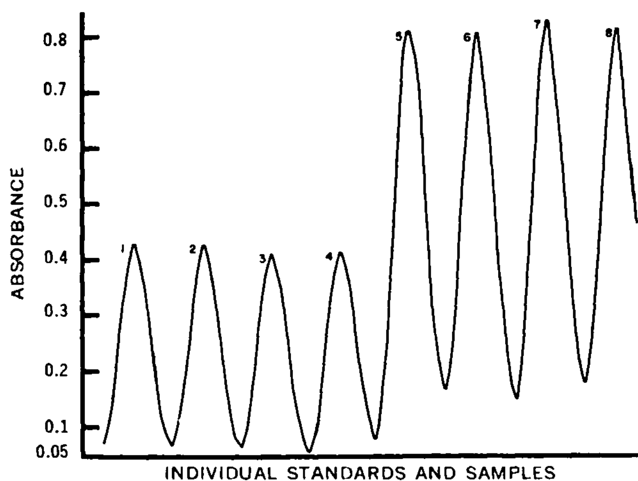

Figure 6—*Typical scans for glyceryl guaiacolate standards and samples. Key: standards, numbers 3, 4, 5, and 6; and samples, numbers 1, 2, 7, and 8.*

formulations containing other active ingredients, such as chlorpheniramine maleate, which would interfere with the colorimetric determination of dextromethorphan hydrobromide.

In the developed automated procedure, an aliquot of the sample was diluted with water and a portion was placed into the sample cups. An aliquot was automatically aspirated, acidified with 1 *N* hydrochloric acid, and extracted with petroleum ether, which was discarded after phase separation. A portion of the aqueous phase was then made alkaline with 1 *N* sodium hydroxide, and the three components were extracted into chloroform. After phase separation, the chloroform stream was divided into three segments by the stream-splitting technique.

One segment of the chloroform-extracted sample was used for formation of the dextromethorphan hydrobromide ion-pair with bromcresol green at pH 5.3, extraction of the complex into the chloroform phase, and measurement at 420 nm. The second segment was utilized for the colorimetric determination of glyceryl guaiacolate. After extraction and phase separation, the chloroform, lower phase, was discarded and the upper phase was passed through a heating bath (60°) for color development. The solution was cooled to room temperature and the resultant color was measured at 555 nm. An alternative extraction procedure was utilized instead of evaporating the chloroform extract to dryness with an in-line evaporator-digestor. Glyceryl guaiacolate was extracted into the sulfuric acid–methanol-water and formaldehyde–methanol reagents. A combination of sulfuric acid-methanol water (60:20:20) was found to yield an efficient phase separation. The third segment of the chloroform stream was used for the colorimetric determination of phenyl-

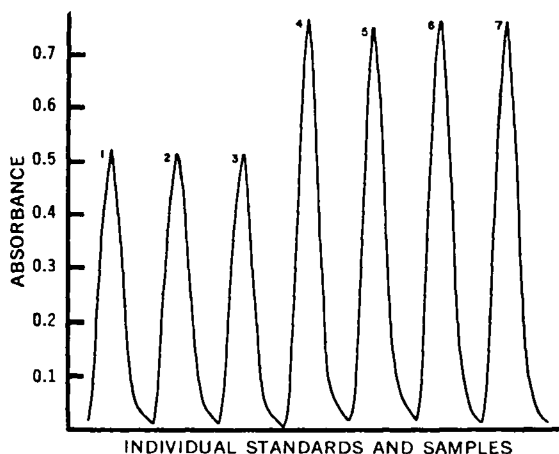

Figure 5—*Typical scans for dextromethorphan hydrobromide standards and samples. Key: standards, numbers 3, 4, and 5; and samples, numbers 1, 2, 6, and 7.*

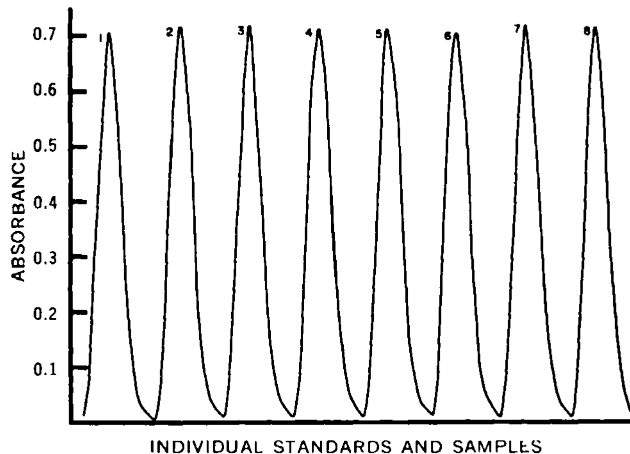

Figure 7—*Typical scans for phenylpropanolamine hydrochloride standards and samples. Key: standards, numbers 1 and 6; and samples, numbers 2, 3, 4, 5, 7, and 8.*

propanolamine hydrochloride. After extraction of the phenylpropanolamine from chloroform into pH 5 citrate buffer and separation of the phases, the chloroform was discarded and a portion of the aqueous phase was mixed with ninhydrin reagent. This mixed stream was passed through a heating bath (95°) for color development, cooled to room temperature, and measured at 570 nm.

The developed simultaneous automated system significantly reduced the analysis time. Previously, about 8 and 12 hr. were required to perform the comparable manual procedures for two-component and three-component preparations, respectively. Based on a single-lot determination with the automated procedure, the time required for analysis was 3 hr. This represented a time savings of 5-9 hr., depending on the number of components present. Since the automated system is capable of analyzing 20 samples/day in duplicate, a reduction in analytical time to 0.4 hr./sample can be realized.

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Molecular-Scale Drug Entrapment as a Precise Method of Controlled Drug Release IV: Entrapment of Anionic Drugs by Polymeric Gelation

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Abstract ☐ A physicochemical approach to the preparation of drug-containing matrix systems is described in which a soluble anionic drug may be entrapped on a molecular scale in coagulated (gelled) polymer emulsion systems. The resultant dried product (or drug-xerogel system) was designed to provide controlled, prolonged release. The phenomenon of gelation of the polymer emulsions by the addition of a divalent cation (Mg^{+2}) was utilized for the entrapment of various drug materials. A solid, highly reproducible entrapment compound of sodium phenobarbital, magnesium sulfate, and a styrene-acrylic copolymer latex was prepared and subjected to *in vitro* and *in vivo* prolonged-release studies. The physical factors influencing both entrapment and drug release were investigated. A significantly increased duration of therapeutic effectiveness was established by the *in vivo* results. Rats, fed dry polymer powder in their diet, exhibited no toxic effects in a 27-day study. The validity and reproducibility of the entrapment procedure were demonstrated.

Keyphrases ☐ Polymer emulsion systems—entrapment of anionic drugs by gelation, prolonged-release rates, methods, prepared with sodium phenobarbital, tested in rats ☐ Timed-release formulations—molecular-scale drug entrapment as a precise method of controlled drug release, anionic drugs by polymeric gelation, prepared with sodium phenobarbital, release rates, rats ☐ Gelations, polymeric—entrapment of anionic drugs (sodium phenobarbital), methods of preparation, release rates, tested in rats ☐ Phenobarbital—prolonged-release formulation prepared by molecular-scale drug entrapment, release rates, rats ☐ Anionic drugs—prolonged-release sodium phenobarbital formulation prepared by molecular-scale drug entrapment, release rates, rats ☐ Drug release—sodium phenobarbital from a prolonged-release formulation prepared by molecular-scale drug entrapment (polymeric gelation), rats

The inclusion of soluble drugs in insoluble matrixes is well known as a means of controlling drug release rates from solid dosage forms. Diffusional models describing drug release from such systems were thoroughly described by T. Higuchi (1) and W. Higuchi (2). Systems have been designed in which "channeling agents" are added to the matrix to attract fluid into the system as well as to facilitate drug diffusion from the matrix (3). Recently, others described (4) the use of dry gels of cross-linked polymer which are charged by immersion in solutions of the drug. Charging of drugs into cross-linked polymers offers a unique method of releasing drug into the eye for very long periods from soft lens systems or other ocular inserts (5). Other drug release systems from matrixes have obvious application for intrauterine and assorted implantable devices, which might range from being totally insoluble to completely soluble or biodegradable.

In previous papers in this series (6-10), it was demonstrated that cationic drug materials could be entrapped in the solid matrix of a flocculated (linear acrylic acid-methacrylic acid copolymer) polymer emulsion system[1] in such a manner as to exhibit reproducible control of drug release and prolongation of drug action from the resultant dried material. The advantages of polymer emulsion systems for this purpose include a high solids

[1] Acrysol ASE 75, Rohm and Haas Co., Philadelphia, Pa.