Colorimetric Determinations of Chlorpheniramine Maleate, Ephedrine Hydrochloride, and Guaiacolsulfonate Potassium in a Cough Syrup

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Abstract □ Colorimetric methods for the quantitative determinations of chlorpheniramine maleate, ephedrine hydrochloride, and guaiacolsulfonate potassium in a cough syrup containing color (amaranth) are reported. Chlorpheniramine maleate can be assayed using the cyanogen bromide method as reported in the literature. Ephedrine hydrochloride can be assayed using a dye method in which interference from chlorpheniramine maleate is taken into consideration. Guaiacolsulfonate potassium can be assayed by coupling it with 4-aminoantipyrine (the method is similar to the one for phenylephrine hydrochloride). All of the methods are simple, accurate, and precise. The application of the guaiacolsulfonate potassium assay method to commercial dosage forms is reported.

Keyphrases □ Chlorpheniramine maleate—colorimetric determination in cough syrups □ Ephedrine hydrochloride—colorimetric determination in cough syrups □ Guaiacolsulfonate potassium—colorimetric determination in cough syrups

Many cough syrups contain an antihistamine such as chlorpheniramine maleate, a bronchodilator such as ephedrine hydrochloride, and an expectorant such as guaiacolsulfonate potassium. The USP method (1) for the analysis of chlorpheniramine maleate in elixir and the NF methods for the analysis of ephedrine hydrochloride (2) and guaiacolsulfonate potassium (3) are not applicable for quantitative determinations due to interference of one active ingredient with the other. The purposes of these investigations were to develop a colorimetric method for the quantitative determination of guaiacolsulfonate potassium (I) and to modify calculations in the previously reported dye method (4) for the analysis of ephedrine hydrochloride (II). These modifications were necessary due to the interference from chlorpheniramine maleate (III), since it could be accurately determined by the cyanogen bromide method (5).

A colorimetric method for the determination of guaiacolsulfonate potassium (6) was not used because of a lack of reproducibility. Another colorimetric method (7) was not preferred due to a lack of sensitivity, since it is important to dilute the syrup as much as possible before the analysis to prevent interference from the coloring agent. The method developed in these investigations is based on oxidizing I with potassium ferricyanide in an alkaline borate buffer solution and then coupling it with 4-aminoantipyrine; the method is similar to that reported for the determination of phenylephrine hydrochloride (8).

Table I—Assay Results on Cough Syrup

Experiment	Assay Results, % of Claim		
	I	II	III
1	100.87	98.45	99.16
2	100.34	99.66	99.56
3	100.00	99.12	100.04
Average	100.40	99.08	99.59
Average deviation	±0.44	±0.42	±0.30

Table II—Assay Results on Guaiacolsulfonate Potassium in Commercial Dosage Forms

Product	Percent of Label Claim Found[a]
Expectorant I	101.38
Expectorant II	99.23
Expectorant III	122.35[b]
Expectorant IV	101.77

[a] Average of three results. [b] Results are high due to interference from phenylephrine hydrochloride.

EXPERIMENTAL

Chemicals and Reagents—All chemicals and reagents were USP, NF, or ACS grade. Chlorpheniramine maleate[1], ephedrine hydrochloride[2], guaiacolsulfonate potassium[2], cherry flavor[3], and coloring agent (amaranth[4]) were purchased and used without further purification.

Preparation of Cough Syrup—The cough syrup was prepared from two stock solutions. The aqueous stock solution contained 4.0 g of guaiacolsulfonate potassium, 200 mg of chlorpheniramine maleate, 500 mg of ephedrine hydrochloride, 50 ml of distilled water, and 190 ml of syrup USP. The alcoholic stock solution contained 12.5 mg of methylparaben, 5 mg of propylparaben, 25 mg of amaranth, 1.0 ml of chloroform, 0.6 ml of cherry flavor, and 2.5 ml of alcohol. The aqueous and alcoholic stock solutions were mixed together and brought to a volume of 250 ml with distilled water.

Preparation of Solutions—The following standard solutions were prepared: 40.0 μg/ml of III in approximately 0.25 *N* HCl; 4.0 μg/ml of III in distilled water; 10.0 μg/ml of II in distilled water; 10.0 μg/ml of II plus 4.0 μg/ml of III in distilled water; and 150.0, 200.0, 250.0, and 300.0 μg/ml of I in distilled water.

The cyanogen bromide solution was prepared by decolorizing bromine TS with 10% potassium cyanide solution.

A buffer solution containing sulfanilic acid and sodium acetate for the analysis of III was prepared according to a reported procedure (5), as was a 1×10^{-4} *M* solution of bromothymol blue in phosphate buffer solution (pH 6.2) (4).

The following aqueous solutions were prepared fresh daily: a 2% solution of sodium borate (buffer for the analysis of I), a 3% solution of 4-aminoantipyrine, and a 4% solution of potassium ferricyanide. Assay solutions for the analysis of I and II were prepared by diluting 10.0 ml of the cough syrup to 100.0 ml with water and then diluting 5.0 ml of the 1:10 dilution to 100.0 ml with water. For III, 5.0 ml of cough syrup was diluted to 100.0 ml with approximately 0.25 *N* HCl.

Preparation of Calibration Curve for Guaiacolsulfonate Potassium—A 2.0-ml quantity of each standard solution was mixed with 1 ml of potassium ferricyanide solution in a 50-ml volumetric flask. The volume was brought to approximately 48 ml

[1] Schering Corp., Bloomfield, N.J.
[2] Merck & Co., Rahway, N.J.
[3] Dolco cherry No. 5225 imitation, Dodge & Olcott, Inc., New York, N.Y.
[4] Hartman Leddon Co., Philadelphia, Pa.

with sodium borate buffer solution, and the solution was mixed. A 1-ml aliquot of 4-aminoantipyrine solution was then added, and the mixture was brought to volume with borate buffer and mixed. The absorbance of each clear solution was determined[5] at 500 nm against a reagent blank prepared by substituting water for the standard solution. Beer's law was followed.

Assay Procedure for Guaiacolsulfonate Potassium—The same procedure was followed except that 5.0 ml of the assay preparation was used for the analysis instead of 2.0 ml of the standard solution. Since Beer's law was followed, the results (Table I) were calculated using the following equation:

$$\frac{A_a}{A_s} \times 10 = \mu g/ml \text{ of I} \qquad \text{(Eq. 1)}$$

where A_a = absorbance of the assay solution, and A_s = absorbance (0.426) of a standard solution that provides 10 μg/ml of I in a 50-ml volumetric flask.

Assay Procedure for Chlorpheniramine Maleate—A 1.0-ml quantity of the standard solution (in 0.25 *N* HCl) and 1.0 ml of the assay preparation were mixed (separately) with 7.0 ml of the buffer solution and 3.0 ml of cyanogen bromide solution and then allowed to stand for 30 min. The absorbance of each solution was measured at 480 nm against a reagent blank prepared by substituting 1.0 ml of 0.25 *N* HCl for the standard solution. Since Beer's law was followed, the results (Table I) were calculated as follows:

$$\frac{A_a}{A_s} \times 100 = \% \text{ of label claim} \qquad \text{(Eq. 2)}$$

where A_a = absorbance of the assay solution, and A_s = absorbance of the standard solution.

Assay Procedure for Ephedrine Hydrochloride—To five different separators, each containing 5.0 ml of bromothymol blue solution and 10.0 ml of chloroform, the following solutions were added: 5.0 ml of distilled water (reagent blank), 5.0 ml of standard aqueous solution of II (A_s), 5.0 ml of standard aqueous solution of II plus III (A_{sc}), 5.0 ml of standard aqueous solution of III (A_c), and 5.0 ml of assay preparation (A_a). Each separator was shaken for 60 sec, layers were allowed to separate, and the absorbance of each clear chloroform layer was measured at 420 nm against the reagent blank.

The absorbance of A_{sc} was equal to $A_s + A_c$. The corrected absorbance value (A_{cc}) due to chlorpheniramine maleate in the assay preparation was determined as follows:

$$A_{cc} = A_c \times \frac{\% \text{ of III present (from Table I)}}{100} \qquad \text{(Eq. 3)}$$

The A_{cc} was subtracted from the A_a value to get the corrected absorbance value (A_{ac}) due to ephedrine hydrochloride in the assay preparation. Since Beer's law was followed (5), the results (Table I) on II were calculated as follows:

$$\frac{A_{ac}}{A_s} \times 100 = \% \text{ of label claim} \qquad \text{(Eq. 4)}$$

Application of Assay Procedure for Guaiacolsulfonate Potassium to Commercial Dosage Forms—The assay procedure for guaiacolsulfonate potassium was tested on four commercial products.

Expectorant I[6] contained, per 5 ml: 10 mg of codeine sulfate, 0.5 mg of menthol, 3.75 mg of bromodiphenhydramine hydrochloride, 8.75 mg of diphenhydramine hydrochloride, 80 mg of guaiacolsulfonate potassium, 80 mg of ammonium chloride, and 5% alcohol.

Expectorant II[7] contained, per 5 ml: 10 mg of codeine phosphate, 5 mg of promethazine hydrochloride, 0.01 ml (0.17 minims) of ipecac fluidextract, 0.015 ml (0.25 minims) of chloroform, 44 mg of guaiacolsulfonate potassium, 66 mg of citric acid, 197 mg of sodium citrate, and 7% alcohol.

Expectorant III[8] contained 5 mg/5 ml of phenylephrine hydrochloride in addition to the ingredients contained in Expectorant II. Expectorant IV[8] (a pediatric product) contained 7.5 mg/5 ml of dextromethorphan hydrobromide instead of 10 mg of codeine phosphate as in Expectorant II.

For the analysis of guaiacolsulfonate potassium, 4.0 ml of Expectorant I was diluted to 250 ml while 7.0 ml each of the other expectorants was diluted to 250 ml with water. A 2.0-ml quantity of the diluted expectorant was mixed with 1 ml of potassium ferricyanide solution in a 50-ml volumetric flask. The rest of the procedure was the same as reported under *Preparation of Calibration Curve for Guaiacolsulfonate Potassium*. In separate experiments, it was determined that there was no interference from other ingredients except phenylephrine hydrochloride, which was present in Expectorant III with codeine. The results, calculated using Eq. 1, are presented in Table II.

DISCUSSION

The results indicate that all three active ingredients of a cough syrup, guaiacolsulfonate potassium, ephedrine hydrochloride, and chlorpheniramine maleate, can be assayed accurately (Table I) using colorimetric methods. All three methods are simple, accurate, and precise. There is no interference from the other active or inactive ingredients, except from chlorpheniramine maleate in the assay procedure for ephedrine hydrochloride. This interference can be taken into consideration easily as explained under *Experimental*.

The new technique for the analysis of guaiacolsulfonate potassium (coupling with 4-aminoantipyrine) follows Beer's law and is rapid (10 min/assay after the standard curve is prepared). The assay method for the analysis of guaiacolsulfonate potassium can be applied to a number of commercial dosage forms (Table II) containing other ingredients such as codeine, menthol, dextromethorphan, promethazine, bromodiphenhydramine, diphenhydramine, and ammonium chloride. Phenylephrine hydrochloride does interfere, which was expected (8).

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[5] A Bausch & Lomb Spectronic 20 was used.

[6] Ambenyl, Parke, Davis & Co., Detroit, Mich.

[7] Phenergan, Wyeth Laboratories, Philadelphia, Pa.

[8] Phenergan VC, Wyeth Laboratories, Philadelphia, Pa.