# Quantitative Determinations of Phenylephrine and Phenylpropanolamine Hydrochlorides in Combination

BHAMY B. SHENOY and V. DAS GUPTA▲

**Abstract** □ The quantitative determinations of phenylephrine and phenylpropanolamine hydrochlorides in combination are reported. Phenylephrine hydrochloride is assayed using the Koshy–Mitchner method without interference from phenylpropanolamine hydrochloride. Phenylpropanolamine hydrochloride is assayed using an acid-dye technique with negligible interference from phenylephrine hydrochloride. Beer's law is followed, and the best pH range for the extraction of the propanolamine–dye complex was determined to be 5.8–6.4. Buffer concentration does not appear to have any effect on the sensitivity of the assay method. In both assay methods, there is no interference from the antioxidant, sodium metabisulfite, and the preservatives, methylparaben and propylparaben.

**Keyphrases** □ Phenylephrine and phenylpropanolamine hydrochlorides in combination—analysis using the Koshy–Mitchner method and acid-dye technique □ Phenylpropanolamine and phenylephrine hydrochlorides in combination—analysis using Koshy–Mitchner method and acid-dye technique □ Drug mixtures —analysis of phenylephrine ahd phenylpropanolamine hydrochlorides in combination

The biggest challenge to a pharmaceutical analyst is how to assay one active ingredient in the presence of another. One such problem arises when two decongestants, phenylephrine hydrochloride (I) and phenylpropanolamine hydrochloride (II), are mixed together. The quantitative determinations of I and II in separate formulations have been reported by many workers (1–5). Ponder (6) reported a column chromatography technique for the separation of I from codeine, dextromethorphan, and II. Recently, Brown and Portmann (7) reported a modified version of the periodate technique of Chafetz (3) for the analysis of these two decongestants in combination in a mixture with aspirin. According to these authors, the method requires: "...careful adjustment of pH, [for] selective separation of two oxidative compounds, benzaldehyde and *m*-hydroxybenzaldehyde..."

The purpose of this paper is to report simple and accurate methods for the analysis of I and II in combination without prior separation. Compound I can be assayed by the Koshy–Mitchner method (2), and Compound II can be assayed by an ion-pair extraction technique using an acid dye, bromthymol blue.

## EXPERIMENTAL

**Chemicals and Reagents**—All of the chemicals and reagents used were USP, NF, or ACS grade. Phenylephrine hydrochloride[1] and phenylpropanolamine hydrochloride[2] were used without further purification.

**Preparation of Buffer Solutions**—Phosphate buffers (0.05 *M*) of various pH values were prepared according to USP XVII (8). The phosphate buffers of other concentrations (0.025, 0.075, 0.1, and 0.125 *M*) were prepared similarly.

**Preparation of Bromthymol Blue Solutions**—Solutions of bromthymol blue ($1 \times 10^{-4}$ *M*) in phosphate buffers of various pH values and concentrations were prepared using a procedure reported earlier (9). The pH of each solution was determined with a pH meter[3].

**Preparation of Standard Solutions of I and II**—Stock solutions of I and II were prepared by dissolving 100 mg. of the powder in enough distilled water to make 250 ml. These stock solutions were used to prepare solutions of lower concentrations as needed.

**Preparation of Assay Solutions of I and II in Combination**—The following three assay solutions were prepared in distilled water using a simple solution method: 1, 0.125% of I and 1% of II; 2, 0.25% of I and 1% of II; and 3, 0.5% of I and 1% of II.

**Determination of Effect of Buffer Concentration on Extraction of Amine–Bromthymol Blue Complexes**—A 5.0-ml. quantity of an appropriate amine salt solution (I, II, chlorpheniramine maleate, or methapyrilene hydrochloride) containing 15 mcg./ml. was mixed with 5.0 ml. of dye solution (pH 6.4) of appropriate buffer concentration, ranging from 0.025 to 0.125 *M* in a 250-ml. separator. A 10.0-ml. quantity of chloroform was added and the mixture was shaken for 60 sec. The phases were allowed to separate, and the absorbance of the clear chloroform layer was determined at 420 nm. A blank was prepared by substituting 5.0 ml. of distilled water for the amine salt solution in the procedure. The results are presented in Fig. 1.

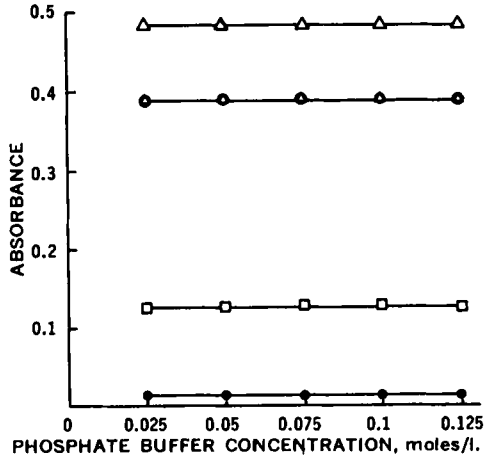


**Figure 1**—*Effect of buffer concentration on extraction of amine–bromthymol blue complexes. Key:* △, *ephedrine–dye complex;* ⊙, *chlorpheniramine–dye complex;* □, *phenylpropanolamine–dye complex; and* ●, *phenylephrine–dye complex.*

[1] Winthrop Laboratories.

[2] S. B. Penick.

[3] Zeromatic.

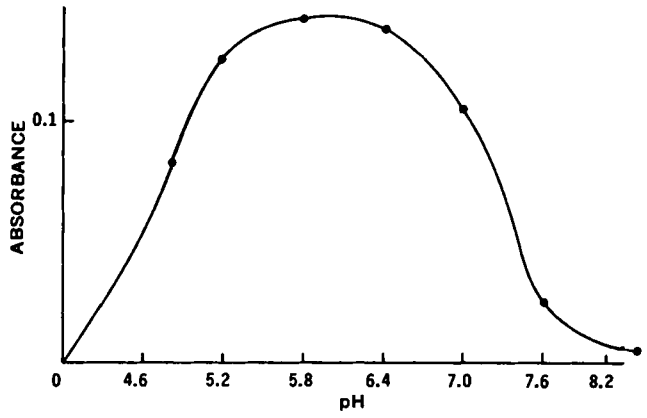


**Figure 2**—*Effect of pH on extraction of phenylpropanolamine–dye complex with chloroform.*

**Determination of Effect of pH on Extraction of II–Bromthymol Blue Complex**—The effect of pH on the extraction of a II–dye complex with chloroform was determined using the procedure reported under *Determination of Effect of Buffer Concentration on Extraction of Amine–Bromthymol Blue Complexes*, except that dye solutions of various pH values in 0.05 *M* phosphate buffer solutions were used. The results are presented in Fig. 2.

**Preparation of Calibration Curve for II**—A 5.0-ml. quantity of an appropriate solution containing various concentrations of II was mixed with 5.0 ml. of a dye solution (pH 6.4) in phosphate buffer (0.05 *M*). Then 10.0 ml. of chloroform was added, and the mixture was treated in the manner described under *Determination of Effect of Buffer Concentration on Extraction of Amine–Bromthymol Blue Complexes*. The results are presented in Fig. 3.

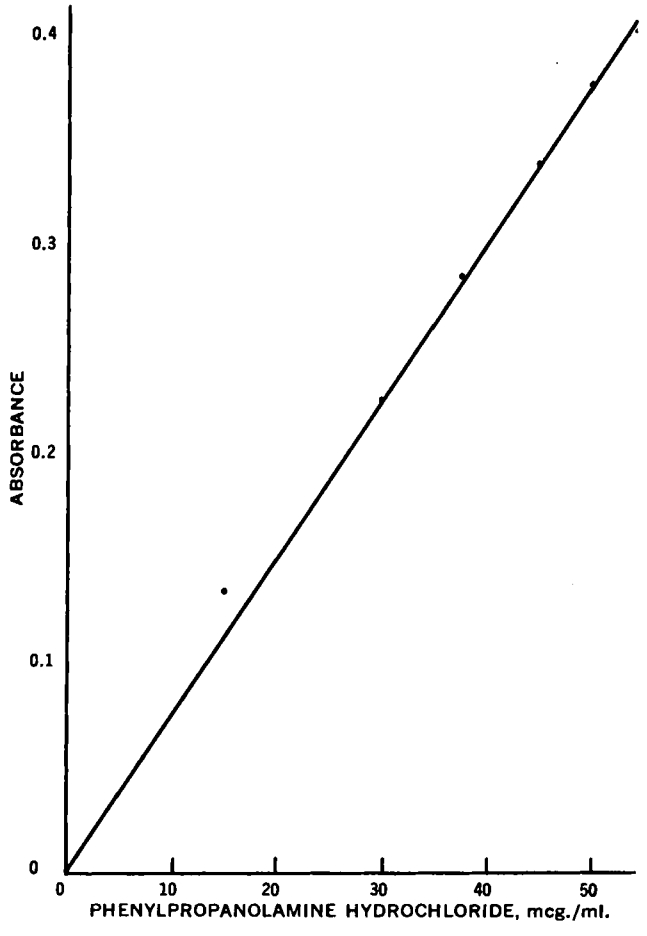


**Figure 3**—*Standard curve for phenylpropanolamine hydrochloride.*

**Table I**—Correction Factors for II

| Solution Number | Factor to be Substracted from Absorbance Value |
|---|---|
| 1 | 0.003 |
| 2 | 0.006 |
| 3 | 0.012 |

**Table II**—Assay Results on I and II

| Solution Number | Results in Percent of Claim I | Results in Percent of Claim II |
|---|---|---|
| 1 | 99.47 | 97.77 |
| | 100.80 | 97.77 |
| | 99.47 | 99.24 |
| | Average 99.91 | Average 98.26 |
| | Avg. dev. ±0.59 | Avg. dev. ±0.65 |
| 2 | 98.15 | 99.29 |
| | 99.47 | 97.77 |
| | 98.15 | 97.77 |
| | Average 98.59 | Average 98.26 |
| | Avg. dev. ±0.59 | Avg. dev. ±0.65 |
| 3 | 100.80 | 100.70 |
| | 100.80 | 97.77 |
| | 99.47 | 100.70 |
| | Average 100.36 | Average 99.72 |
| | Avg. dev. ±0.59 | Avg. dev. ±0.61 |

**Determination of Interference from Sodium Bisulfite, Methylparaben, and Propylparaben**—To determine the interference from the antioxidant, sodium bisulfite, and the preservatives, methylparaben and propylparaben, a solution containing 0.2% of sodium bisulfite, 0.02% of methylparaben, and 0.01% of propylparaben was prepared in distilled water, using a simple solution method. These are the usual concentrations added to nasal drops. The solution was assayed in the same manner as described under *Assay Procedure for II in Combination with I*. This solution was also assayed for I using the Koshy–Mitchner method[4] (2). There was no interference in the assay procedures from the preservatives and the antioxidant.

**Determination of Interference from I**—A solution containing 15.0 mcg./ml. of I was assayed in the same manner as described under *Assay Procedures for I*. There was a minor interference in the assay procedure. The correction factors are presented in Table I.

**Determination of Interference from II**—A solution containing eight times more of II than I was assayed using the Koshy–Mitchner method[4] (2) for the determination of I. There was no interference in the assay procedure.

**Assay Procedure for I**—Compound I was assayed using the Koshy–Mitchner method[4] (2). The results are presented in Table II.

**Assay Procedure for II in Combination with I (Assay Solutions 1, 2, and 3)**—A 5.0-ml. quantity of the appropriately diluted assay solution containing 40.0 mcg./ml. of II was mixed with 5.0 ml. of the dye solution (pH 6.4, buffer concentration 0.05 *M*). Then 10.0 ml. of chloroform was added, and the mixture was treated in the manner described under *Determination of Effect of Buffer Concentration on Extraction of Amine–Bromthymol Blue Complexes*.

**Calculation of Assay Results on II**—Provided that the results on I are within limits as determined above by the Koshy–Mitchner procedure (2), the correction factors reported in Table I are suggested because of a minor interference from I.

After making these corrections, the results were determined with the help of the calibration curve (Fig. 3) (Table II).

## DISCUSSION AND CONCLUSIONS

The assay results (Table II) indicate that II can be assayed using an acid-dye technique. Beer's law is followed within a narrow range of 30–50 mcg./ml. of II (Fig. 3). The interference from I was almost

[4] Using borate buffer.

nil because I is not as strong a base as II since only the latter contains a primary amino group. There was no interference from the antioxidant, sodium bisulfite (0.2%), and the preservatives, methylparaben (0.02%) and propylparaben (0.01%). The best pH range for the extraction of the phenylpropanolamine–dye complex with chloroform appears to be from 5.8 to 6.4 (Fig. 2). A pH value of 6.4 was preferred for these studies due to low blank values. The effect of buffer concentration on the extraction of the complex appears to be negligible (Fig. 1). To confirm this finding, three more amines (chlorpheniramine, ephedrine, and phenylephrine) were tested and the results were identical (Fig. 1). Compound I can be easily assayed (Table II) using the Koshy–Mitchner method (2) with borate buffer without any interference from II, the antioxidant, and the preservatives.

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▲ To whom inquiries should be directed.


# Quantitative GLC Determination of Resorcinol Monoacetate in Dermatological Products


**PRAMOD P. KARKHANIS▲, DAVID O. EDLUND, and JON R. ANFINSEN***



**Abstract** □ A GLC procedure employing an internal standard of orcinol is described for the analysis of resorcinol monoacetate in dermatological preparations. The analysis of a cream or lotion is performed by the addition of an internal standard, acetylation, extraction with benzene, evaporation of benzene, addition of chloroform, and then chromatography on a 5% cyano ethyl silicone column.



**Keyphrases** □ Resorcinol monoacetate creams and lotions—GLC analysis □ Dermatological creams and lotions, resorcinol monoacetate—GLC analysis □ Cream, resorcinol monoacetate—GLC analysis □ Lotion, resorcinol monoacetate—GLC analysis □ GLC—analysis, resorcinol monoacetate in creams and lotions


Due to its mild action, resorcinol monoacetate has been incorporated in dermatological products primarily for the treatment of eczema, psoriasis, and seborrheic dermatitis. In addition to the base, the dermatological preparations frequently contain sulfur, hydrocortisone, and hexachlorophene.

Due to the complex matrix present in dermatological creams and lotions, the quantitative determination of resorcinol monoacetate requires extensive cleanup procedures.

Methods of analysis for resorcinol monoacetate reported in the literature have included UV absorption (1, 2) and photometry after reaction with picric acid (3) or *p*-dimethylaminobenzaldehyde (4). Paper chromatography and TLC techniques have also been used extensively (5, 6), and methods describing the use of GLC for phenolic compounds have been reported (7, 8). None of these methods has been used for the quantitative determination of resorcinol monoacetate in a pharmaceutical matrix.

**Table I**—Statistical Data from GC Analysis of Resorcinol Monoacetate (RMA) in Cream Base Placebo

| RMA Added, mg. | RMA Found, mg. | Bias, mg. | *SD*, mg. | *df* | *CV*, % |
|---|---|---|---|---|---|
| 13.50 | 13.45 | −0.05 | 0.193 | 5 | 1.43 |
| 15.00 | 14.94 | −0.06 | 0.187 | 6 | 1.25 |
| 16.50 | 16.53 | +0.03 | 0.249 | 5 | 3.51 |

The method described here utilizes an internal standard technique and a simple cleanup procedure involving acetylation and extraction. It allows the separation and determination of resorcinol monoacetate by GLC without interference from the excipients commonly present in dermatological creams and lotions. This method can be adapted to the quality control of resorcinol monoacetate in creams and lotions.

## EXPERIMENTAL[1]

**Chromatographic Conditions**—A 1.22-m. (4-ft.), 2-mm. i.d., stainless steel column packed with 5% cyano ethyl silicone on diatomite aggregate (high performance)[2], 80–100 mesh, was used for the assay. The column temperature was 170°, and the detector and injection port temperatures were 220°. The helium carrier gas flow rate was 15 ml./min. A flame-ionization detector was used with a hydrogen flow rate of 30 ml./min. and an air flow rate of 450 ml./min.

**Reagents and Solutions**—The following were used: resorcinol monoacetate NF; orcinol, 95–99% pure[3]; acetic anhydride, reagent grade; and pyridine, reagent grade.

[1] A Hewlett-Packard 7620A research chromatograph with 7127A strip chart recorder and a 7670A automatic sampler was used.

[2] Five percent XE-60 on Chromosorb G (HP), Supelco, Inc., Bellefonte, Pa.

[3] K & K Laboratories, Plainview, NY 11803