DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 13(3), 473-486 (1987)

QUANTITATION OF PHENYLEPHRINE HYDROCHLORIDE IN PHARMACEUTICAL DOSAGE FORMS

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ABSTRACT

A reverse phase high-pressure liquid chromatography method for the quantitation of phenylephrine hydrochloride in a variety of pharmaceutical dosage forms has been developed. The developed method did not require the use of a counter-ion to increase the retention time of phenylephrine. The method is simple, accurate, precise and reproducible with a percent relative standard deviation of 0.54 based on 6 injections. The results were in excellent agreement with the results obtained using a colorimetric method. The separation between phenylephrine, the internal standard and other ingredients is greatly affected by pH changes (between 5.9-6.1) and the particle size of the column materials (5 micron versus 10 micron). A number of other active ingredients brompheniramine maleate, chlorpheniramine maleate, phenylpropanolamine and guaifenesin, etc.) and the excipients such as parabens and sodium benzoate did not interfere with the assay procedure.

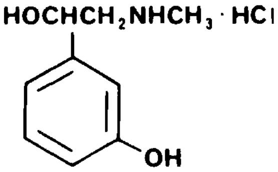

Figure 1 - STRUCTURE OF PHENYLEPHRINE HYDROCHLORIDE

BACKGROUND

Phenylephrine hydrochloride (Figure 1) is extensively used in medicine as a decongestant. Besides the dosage forms containing only phenylephrine hydrochloride, there are hundreds of commercially available products containing a variety of other active ingredients. The most commonly added ingredients are brompheniramine maleate, chlorpheniramine maleate and phenylpropanolamine hydrochoride. In many dosage forms, the excipients such as colors, flavors and preservatives are also added which can interfere with the quantitation of phenylephrine hydrochloride.

LITERATURE SURVEY

Among the methods available for the quantitation of phenylephrine hydrochloride are colorimetric[1], ion pair extraction[2], column chromatography[3,4] separation using cation exchange resin with UV spectroscopy[5] and paired ion HPLC[6]. The USP-NF method[7] for most of the dosage forms requires the preparation of an adsorbant and then column chromatography. For phenylephrine nasal jelly, the USP-NF method[7] is based on HPLC using 80% methanol as the mobile phase. The column chromatographic methods are very tedious and time consuming. The use of 80% methanol as a mobile phase builds up high pressure which can shorten the life of the column. The paired ion HPLC usually shortens the life of the costly column and sometimes causes problems with the windows of the UV detector.

Phenylphrine hydrochloride is a very stable compound. In one study[6], it was found to be stable for 9 days in an aqueous solution at 95°, and in 0.5M HCl/0.5M NaOH for 9 days at 25°. This is why the expiry dates for liquid dosage forms such as elixirs, nose drops, eye drops and injections are usually long.

The purpose of these investigations was to develop a method for the quantitation of phenylephrine hydrochloride based on reverse-phase HPLC without ion-pairing which could be used to analyze a variety of pharmaceutical dosage forms.

MATERIALS AND METHODS

Chemicals and Reagents: All the chemicals and reagents were either USP-NF or ACS grade and used as received. Phenylephrine hydrochloride powder[8] was used without further purification.

Apparatus: The high-pressure liquid chromatograph[9] was equipped with a multiple wavelength UV detector[10] and a recorder[11].

Columns: Two octadecyl columns (30 cm x 3.9 mm i.d.[12] and 25 cm x 4.6 mm i.d.[13]) were used.

Chromatographic Conditions: The mobile phase contained 2% (V/V) of acetonitrile in 0.02M aqueous phosphate buffer (pH 5.9-6.1)[14]. The flow rate was 2.0 ml/min, the sensitivity was set at 0.04 AUFS (271 nm) and the chart speed was 30.5 cm/hr. All studies were conducted at room temperature.

Preparation of Stock Solutions: A 2.0 mg/ml each of stock solutions of phenylephrine hydrochloride and acetaminophen (the internal standard) in water were prepared. A 0.2% solution of aspirin in methanol was prepared fresh as needed. Aspirin was used as the internal standard for a dosage form which contained acetaminophen.

Preparation of Standard Solutions: The standard solutions containing various concentrations of phenylephrine hydrochloride were prepared as needed by diluting the stock solution with water. Before bringing to volume, an appropriate quantity of the stock solution of the internal standard was added. The most commonly used concentrations were 225 μg/ml of phenylephrine hydrochloride, and 120 μg/ml of acetaminophen. When aspirin was used as the internal standard, its concentration was 320 μg/ml.

Preparation of Assay Solutions; Liquid Dosage Forms: An appropriate quantity of the liquid dosage form representing 12.5 mg of phenylephrine hydrochloride was transferred to a volumetric flask (50.0 ml). After adding the internal standard, the mixture was brought to volume with water.

Solid Dosage Forms: Ten tablets were ground to a fine powder and an appropriate quantity of the powder representing 12.5 mg of phenylephrine hydrochloride was weighed accurately. The powder was mixed with 40 ml of water and heated to about 80° for 2-3 minutes in a 150 ml beaker. Preliminary investigations and a literature report[6] indicated that phenylephrine hydrochloride was stable at this temperature for at least 9 days. The mixture was cooled, the internal standard added and brought to volume (50.0 ml) with water.

It was mixed, filtered[15], first 5-7 ml of filtrate rejected and then collected for assay.

Treatment of Phenylephrine Hydrochloride Solution with Acid/Base: To a 10.0 ml portion of phenylephrine hydrochloride solution (0.25 mg/ml) in water, either 1 ml of ∿1N NaOH or 1 ml of ∿1N H_2SO_4 was added. The mixture was boiled for about 5 minutes, cooled, neutralized, brought to volume (10.0 ml) with water and assayed.

Assay Procedure: A 20.0 μl quantity of the assay solution was injected into the chromatograph using the appropriate column and the mobile phase of either pH 5.9, 6.0 or 6.1. For comparison purposes, the standard solution was injected when the assay eluted. The standard solution contained the identical concentrations of the drug and internal standard based on the label claim.

Calculations; Since preliminary investigations indicated that the ratio of peak heights (drug/internal standard) were related to the concentrations of phenylephrine hydrochloride (range tested 2.4 to 6.4 μg), the results were calculated using the following equation:

$$\frac{A_{rph}}{S_{rph}} \times 100 = \text{Percent of the label claim found}$$

RESULTS AND DISCUSSION

The results (Table 2) indicate that phenylephrine hydrochloride can be assayed in a variety of pharmaceutical products using a reverse phase high pressure liquid chromatography without the addition of a counter ion. The results were in agreement (Table 2) with the results of a colorimetric method[1] (Table 2). The ratio of the peak heights (drug/internal standard) were linear between

TABLE 1

List of Dosage Forms Studied

Number	Name	Ingredients (Active) (per ml/per tablet)	Excipients
1	Elixir^a	1.0 mg each of phenylephrine HCl and phenylpropanolamine HCl and 0.8 mg of brompheniramine maleate	Purple color, flavors and preservatives
2	Eye Drops^b	25.0 mg of phenylephrine HCl	Benzolkonium Cl, boric acid, sodium bisulfite and EDTA
3	Liquid^c	Phenylephrine HCl 1.0 mg, phenylpropanolamine HCl 9.0 mg and guaifenesin 40 mg	Asin #1 and orange color
4	Nasal drops^d	2.5 mg of phenylephrine HCl	Parabens and phosphate buffer
5	Nasal drops^d	5.0 mg of phenylephrine HCl	Parabens and phosphate buffer
6	E.C. Nasal Solution^d	2.5 mg of phenylephrine HCl and 20 mg of lidocaine HCl	Parabens and phosphate buffer
7	Tablets^e	15.0 mg each of phenylephrine HCl and phenylpropanolamine HCl and 12 mg of brompheniraminem maleate	Blue color

TABLE 1

List of Dosage Forms Studied

Number	Name	Ingredients (Active) (per ml/per tablet)	Excipients
8	Tablets[f]	5.0 phenylephrine HCl, 2.0 mg chlorpheniramine maleate and 3.25 mg of acetaminophen	Two layers, white and yellow tablets
9	Tablets[g]	Phenylephrine HCl 25 mg, phenylpropanolamine HCl 50 mg, chlorpheniramine maleate 8 mg, hyoscyamine sulfate 0.2 mg, atropine sulfate 0.036 mg and scopolamine HBr 0.012 mg	Green color

[a] Dimetapp by A.H. Robins Pharmaceuticals.
[b] Mydfrin®2.5% by Alcon Laboratories.
[c] Entex by Norwich-Eaton Pharmaceuticals.
[d] Compounded at Ben Taub Hospital, Houston, TX.
[e] Bromatapp by Goldline Laboratories.
[f] Dristan by Whithall Laboratories.
[g] Tuss-Delay by Luchem Pharmaceuticals.

TABLE 2

Assay Results

Number (Table 1)	Name (Table 1)	Percent of the Label Claim Found Using HPLC Method	Percent of the Label Claim Found Using Colorimetric Method
1	Elixir	100.7	101.1
2	Eye drops	100.5	100.8
3	Liquid	100.0	100.0
4	Nasal drops 1/4%	101.2	101.0
5	Nasal drops 1/2%	100.6	100.1
6	E.C. nasal solution	100.8	101.0
7	Tablets (blue)	98.8	98.3
8	Tablets (white & yellow)	100.9	100.5
9	Tablets (green)	99.3	99.5

2.4 to 6.4 μg of phenylephrine hydrochloride. The percent relative standard deviations based on 6 injections was 0.54. A number of other ingredients such as atropine sulfate, brompheniramine maleate, boric acid, chlorpheniramine maleate, colors, hyoscyamine sulfate, EDTA, guaifenesin, parabens, phenylpropanolamine hydrochloride, scopolamine hydrobromide, sodium bisulfite and sodium benzoate did not interfere with the assay procedure (Figures 2-3). The internal standard was acetaminophen for all of the dosage forms studied except one which itself contained acetaminophen (number 8, Table

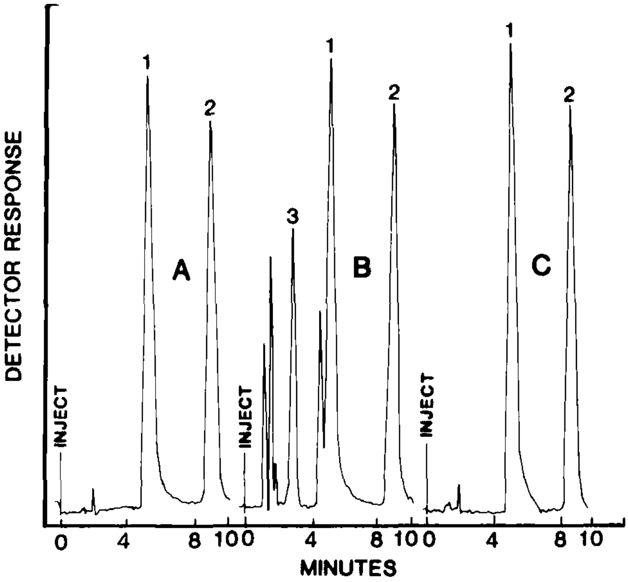

FIGURE 2

Sample chromatograms using column with 10 micron size particles and pH of the mobile phase was 5.9. Peaks 1-3 are from phenylephrine, acetaminophen and sodium benzoate, respectively. All the other peaks are from unidentified excipients. Chromatogram A is from a standard solution; B from an elixir (Table 1) and C from E.C. nasal solution (Table 1). For other chromatographic conditions, see text.

1). For this product, aspirin was used as the internal standard (Figure 3C). When aspirin was used as the internal standard, there was a small separate peak from salicylic acid (peak 5, Figure 3C) which is usually present in aspirin.

It is interesting to point out that the pH (between 5.9 to 6.1) and the columns (10 micron versus 5 micron size particles) affected the separations of ingredients. For example at pH 5.9, phenylephrine and acetaminophen separated better (Figure 3) than at pH 6.0 (Figure 4). Also with 10 micron size particles[12], one

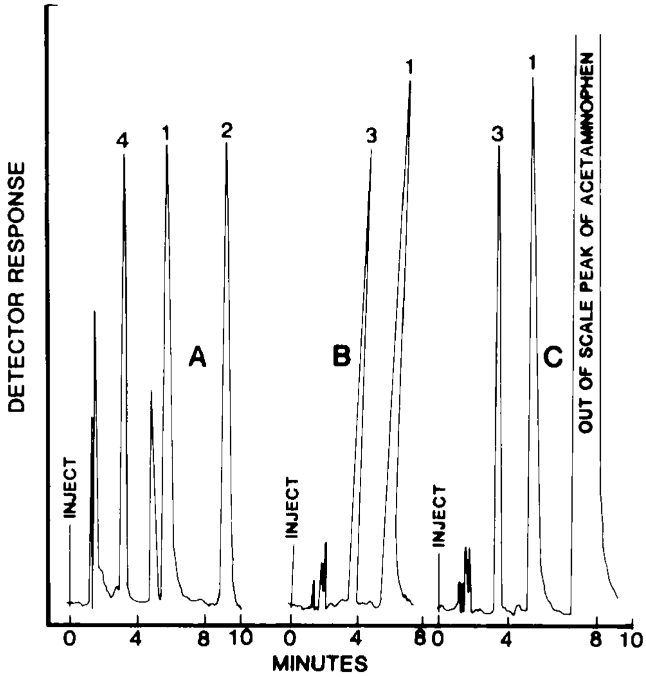

FIGURE 3

Sample chromatograms using column with 5 micron size particles and pH of the mobile phase was 5.9. Peaks 1-5 are from phenylephrine, acetaminophen, aspirin, sodium benzoate and salicylic acid, respectively. All the other peaks are from unidentified excipients. Chromatogram A is from an elixir; B from a standard solution with aspirin as the internal standard and C from a tablet (number 8, Table 1) which contained large quantity of acetaminophen.

inactive ingredient of an elixir (number one in Table 1) did not separate completely from phenylephrine (Figure 2B). With 5 micron size particles[13], the separation was almost complete (Figure 3A). In this elixir, peak 4 (Figures 3-4) was confirmed to be from sodium benzoate.

Furthermore, it is interesting that at pH 6 when the same mobile phase, and same assay and standard solutions were analyzed

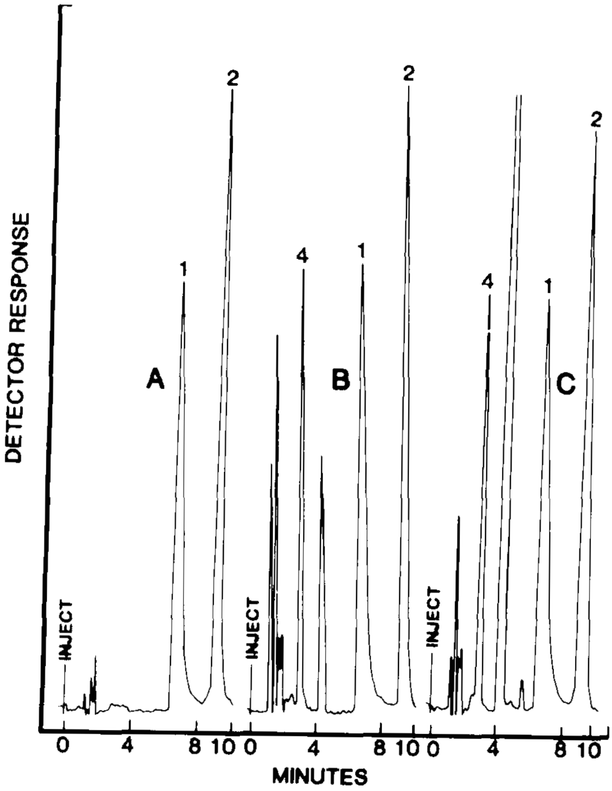

FIGURE 4

Sample chromatograms using same conditions as in Figure 3 except that the pH of the mobile phase was 6. Peaks 1-2 and 4 are from phenylephrine, acetaminophen and sodium benzoate, respectively. All the other peaks are from unidentified excipients. Chromatogram A is from a standard solution; B from an elixir (Table 1) and C from a liquid (Table 1).

using 10 micron size particles[12] and the 5 micron size particles columns, the chromatograms were quite different. For example, one of the inactive ingredients (probably color) eluted before phenylephrine (Figure 4B) when 5 micron size particles[13] were used. The same ingredient eluted after phenylephrine (Figure 5B) when 10 micron size particles[12] were used. Since both columns were of

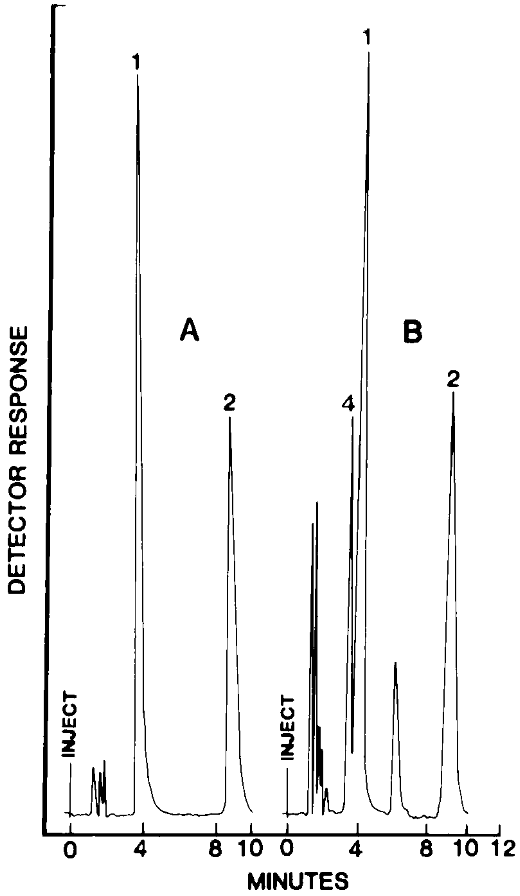

FIGURE 5

Sample chromatograms using 10 micron size particles column and the mobile phase with pH 6.0. Peaks 1-2 and 4 are same as in Figure 4. All the other peaks are from unidentified excipients. Chromatogram A is from a standard solution and B from an elixir (Table 1).

octadecyl materials, this behavior cannot be easily explained. With 10 micron size particles[12] at pH 6, sodium benzoate (peak 4, Figure 5B) did not separate from phenylephrine hydrochloride. With 5 micron size particles[13], this separation was complete (Figure 4B, peak 4). Finally, at pH 6.1, using 5 micron size particles, the separation between phenylephrine (whose retention time had increased) and acetaminophen (the internal standard) was very poor. For best results, the authors recommend the use of pH between 5.9-6.0 for the mobile phase and 5 micron size particles column[13]. The phenylephrine solutions which were treated with sodium hydroxide/sulfuric acid, did not show much decomposition. Only solution which was treated with sodium hydroxide lost about 2% of the potency and showed very small new peaks in the chromatogram. Phenylephrine appears to be a very stable compound as has been reported earlier in the literature[6].

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