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QUANTITATION AND STABILITY OF VERAPAMIL HYDROCHLORIDE USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A high-performance liquid chromatography method for the quantitation of verapamil hydrochloride in pharmaceutical dosage forms has been developed. The method is precise and accurate with a relative standard deviation of 0.63% based on six injections. No preliminary extraction procedure is required to assay injections and a very simple extraction procedure is needed for tablets. There is no interference from the excipients and the method appears to be stability-indicating. The optimum pH range of stability is about 3.2 to 5.6 and the phosphate buffer and ionic strength have very little effect on the stability. Verapamil hydrochloride appears to be a very stable compound since in 105 days at 50°, the aqueous solutions (0.5 mg/ml) did not decompose.

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BACKGROUND

Verapamil hydrochloride is an antiarrhythemic agent which is extensively used in medicine. The analytical literature for the quantitation of verapamil was reviewed by Watson and Kapur[1]. The two high-performance liquid chromatography methods reported[1,2] in the literature require a fluorophotometric detector which is not commonly available. These methods are applicable to the quantitation of verapamil in biological fluids. The purpose of these investigations was to develop a stability-indicating assay procedure for the quantitation of verapamil in pharmaceutical dosage forms using high-performance liquid chromatography and a UV detector. The method was also used to study the stability of verapamil hydrochloride in aqueous solutions.

MATERIALS AND METHODS

Chemicals and Reagents: All the chemicals and reagents were USP, NF or ACS quality and used without further purification. The verapamil hydrochloride[3] powder was used as received.

Apparatus: The high pressure liquid chromatograph[4] was equipped with a multiple wavelength UV detector[5] and a recorder[6].

Columns: A semipolar column[7] (30 cm x 4 mm i.d.) and a nonpolar column[8] (30 cm x 4 mm i.d.) were used.

Chromatographic Conditions: The mobile phase one which was an aqueous solution of 0.02M KH_2PO_4 containing 38% V/V of acetonitrile was used with the semipolar column. The mobile phase two which contained 49% methanol (V/V), 0.45% glacial acetic acid (V/V) and 0.036 M ammonium formate in water was used with the

nonpolar column. The flow rate was 2.4 ml/min (2.0 ml/min for the nonpolar column) and the temperature was ambient. The sensitivity was set at 0.04 AUFS (278 nm) and the chart speed was 30.5 cm/hr. The sensitivity was 0.2 AUFS with the nonpolar column.

Preparation of Stock and Standard Solutions: The stock solution of verapamil hydrochloride (2.5 mg/ml) and dextromethorphan hydrobromide (5.0 mg/ml) in water were prepared fresh daily. The standard solutions were prepared as needed by diluting the stock solutions with water. For assays, the concentrations of verapamil hydrochloride and dextromethorphan hydrobromide (the internal standard) were 250 and 200 μg/ml, respectively. For nonpolar column, the concentration of verapamil hydrochloride was 0.5 mg/ml in water.

Preparation of Assay Solutions From Vials: Mix an aliquot of the solution containing 12.5 mg of verapamil hydrochloride with 2.0 ml quantity of the stock solution of dextromethorphan hydrobromide (the internal standard) and bring to volume (50.0 ml) in a volumetric flask.

Extraction Procedure from Tablets: Weigh 10 tablets accurately and grind them to a fine powder. If content uniformity is to be determined, then grind single tablet to a fine powder. Weigh accurately powder representing 25.0 mg of verapamil hydrochloride and mix it with approximately 90 ml of water in a 150 ml beaker. Add 4.0 ml of the stock solution of dextromethorphan hydrobromide and stir occasionally during 15 minutes. Transfer the mixture to a 100 ml volumetric flask and bring to volume with water. Filter

the mixture[9] and reject first 25 ml of the filtrate and then collect a portion for analysis.

Preparation of Solutions for Stability Studies: A number of solutions of various pH values were prepared for stability studies (Table 1). After zero day data (assays, pH values[10] and physical appearances), the solutions were transferred to 60 ml amber colored bottles[11] and stored at 50° (± 1) in an electric oven. At appropriate intervals (39, 81 and 105 days), the data were recorded again.

Sample of Decomposed Solution: A 10.0 ml quantity of the stock solution of verapamil hydrochloride was mixed with 5 ml of ∿1N NaOH solution in a 150 ml beaker. The mixture was heated to boiling on a hot plate for ∿50 minutes, replacing water as needed. The mixture was then cooled and pH adjusted between 3-4 with ∿0.5N HCl and brought to volume (100.0 ml) with water in a volumetric flask.

Assay Procedure: A 20 µl aliquot of the assay solution was injected into the chromatograph at the conditions described (Mobile phase 1 and semipolar column). For comparison, a 20 µl aliquot of the standard solution containing identical concentrations of verapamil hydrochloride and dextromethorphan hydrobromide was injected after the assay eluted. For stability studies, both columns with appropriate chromatographic conditions, as described above, were used. No internal standard was used with the nonpolar column since the solution was injected directly without dilution (AUFS 0.2).

Calculations: Since preliminary investigations indicated that

TABLE 1

Composition of Aqueous Solutions of Verapamil Hydrochloride (0.5 mg/ml) Prepared for Stability Studies

Solution #	pH (± 0.05)	Buffering Agent (M)	Ionic Strength[a]
1	1.4	HCl (0.08)	0.23
2	3.2	Phosphate (0.08)	0.23
3	4.3	Phosphate (0.08)	0.23
4	5.6	Phosphate (0.08)	0.23
5	6.5	Phosphate (0.08)	0.23
6	7.3	Phosphate (0.08)	0.23
7	7.3	Phosphate (0.06)	0.23
8	7.3	Phosphate (0.10)	0.23
9	7.3	Phosphate (0.08)	0.17
10	7.3	Phosphate (.08)	0.32

[a]Adjusted with KCl.

ratio of the peak heights of verapamil and dextromethorphan hydrobromide were directly related to the concentration of verapamil (range tested 2.5 - 7 µg), the results were calculated using the equation:

$$\frac{R_{pha}}{R_{phs}} \times 100 = \text{Percent of the label claim found}$$

where R_{pha} is the ratio of peak heights of drug/internal standard of the assay solution and R_{phs} that of the standard solution. For

the nonpolar column, peak height of the standard solution was compared with the peak height of the assay solution.

RESULTS AND DISCUSSION

The solutions of verapamil (Table 1) did not decompose in 105 days at 50° which is approximately equal to 4.5 years (using an approximate factor of 3 with each 10° change in temperature) at 25°. There was very slight decomposition (less than 5%) at pH values of 1.4, 6.5 and 7.3. The optimum pH of stability appears to be a broad range from about 3.2 to 5.6. The manufacturer recommended[12] pH range for injectables is between 4.1-6. The results of these studies indicate that phosphate buffer and the ionic strength (Solution 6-10, Table 1) had very little effect on the stability of verapamil hydrochloride. The stability assay results were also determined using a different column (μC_{18}) with a different mobile phase, methanol with ammonium formate (see chromatographic conditions). The assay results using both chromatographic conditions were similar. The pH values and the physical appearances of these solutions did not change during 105 days of study.

The assay results determined using the semipolar column (Table 2) indicate that the developed method can be used for the quantitation of verapamil hydrochloride in pharmaceutical dosage forms. The method is accurate and precise with an average relative standard deviation of 0.63% based on six readings. The concentration of verapamil hydrochloride was directly related to the ratio of peak heights of verapamil/dextromethorphan (Figure 1) between 2.5 to 7 μg range.

TABLE 2

Assay Results

Dosage Form	Verapamil HCl mg/ml or mg/tab	Percent of the Label Claim Found
Injectable 1	2.5	101.3
Injectable 2	2.5	104.0
Injectable 3	2.5	102.7
Tablets 1 (Average of 10)	80	99.0
Tablets 2 (Average of 5) Different Lot and Manufacturer	80	96.5
Single Tablet 1	80	96.1
Single Tablet 2	80	97.2
Single Tablet 3	80	102.4
Single Tablet 4	80	103.7
Single Tablet 5	80	98.2
	Recovery Data From Synthetic Solutions	
Synthetic Solution 1	2.0	100.1
Synthetic Solution 2	1.0	100.1

No preliminary extraction procedure was required to assay the injectable. A very simple extraction procedure was needed to quantify verapamil in tablets. The coloring matter and excipients present in the tablets did not interfere with the assay procedure (Figure 2).

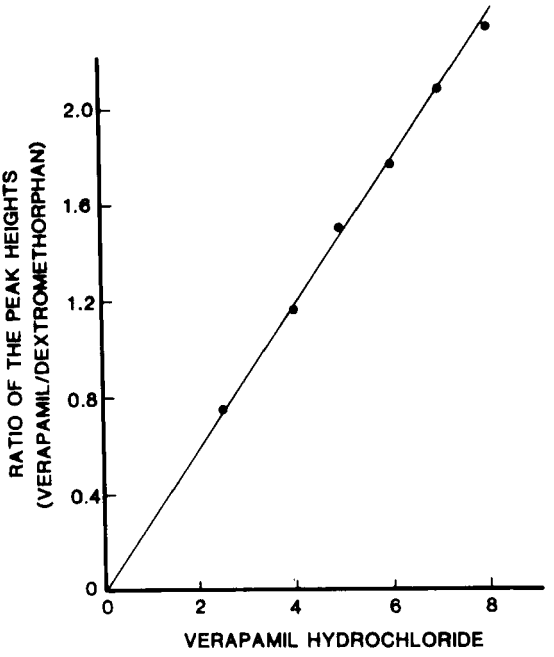

FIGURE 1

Standard curve of concentrations of verapamil hydrochloride versus ratio of the peak heights of verapamil/dextromethorphan using the semipolar column.

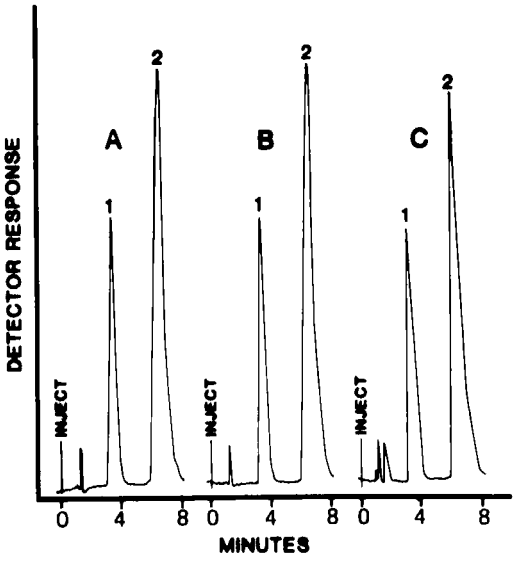

FIGURE 2

Sample Chromatograms. Peaks 1-2 are from dextromethorphan (the internal standard) and verapamil, respectively. Chromatogram A is from a standard solution, B from an injectable 2 (Table 2) and C from tablets 1 (Table 2). For chromatographic conditions, see text. The semipolar column was used.

The method is stability indicating since a sample decomposed by using heat and sodiuum hydroxide (see Experimental) for ∿50 min showed 60.3% potency. No new peaks in the chromatograms were recorded. The decomposition product(s) formed a gummy white mass insoluble in water. The mass accumulated in the beaker (sticking to the bottom) as the time allowed for degradation was increased. After one min of heating there was no decomposition. All the precipitate formed on adding sodium hydroxide redissolved upon the addition of hydrochloric acid. After 50 min of heating, the gummy mass described above did not dissolve. This mass was soluble in methanol.

The developed method can be used to assay verapamil in dosage forms and also to test the content uniformity of tablets.

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4. ALC 202 equipped with U6K Universal Injector, Waters Assoc., Milford, MA.
5. Spectroflow monitor 770, Schoeffel Instruments, Ramsey, NJ.
6. Omniscribe 5213-12, Houston Instruments, Austin, TX.
7. μBondapak Phenyl, Waters Associates, Milford, MA.
8. μBondapak C_{18}, Waters Associates, Milford, MA.
9. Whatman #1 filter paper.

10. Determined with SS-3 Zeromatic pHmeter, Beckman Instruments, Fullerton, CA.

11. Brockway Glass Co., Brockway, PA.

12. Isopten® for Intravenous Injection, Notes for the Physicians, Print #1063, Knoll Pharmaceutical Co., Whippany, NJ 07981, June, 1981.