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QUANTITATION OF RANITIDINE HYDROCHLORIDE IN TABLETS AND INJECTIONS USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A stability-indicating reverse-phase high-performance liquid chromatography method without the use of a counterion has been developed to quantify ranitidine hydrochloride in pharmaceutical dosage forms. The method is accurate and precise with a percent relative standard deviation of 1.5 based on 5 injections. The extraction procedure for ranitidine from tablets is very simple and there was no interference from the excipients present. Ranitidine appears to be stable to heat on the acidic side and very susceptible to decomposition on the basic side. It lost 84.4% of potency on 20 minute boiling with sodium hydroxide with a new peak in the chromatogram. It lost 37.8% of the potency on treatment with hydrogen peroxide solution for 20 minutes at room temperature with 2 new peaks in the chromatogram.

INTRODUCTION

Ranitidine hydrochloride (Figure 1) is extensively used against hypersecretory conditions or intractable duodenal ulcers. The drug is fairly new and is not yet official in the USP-NF. It is available commercially in the forms of tablets and injection. The HPLC analysis of ranitidine hydrochloride in plasma samples has been reported (1). In this method, the authors used 40° temperature for

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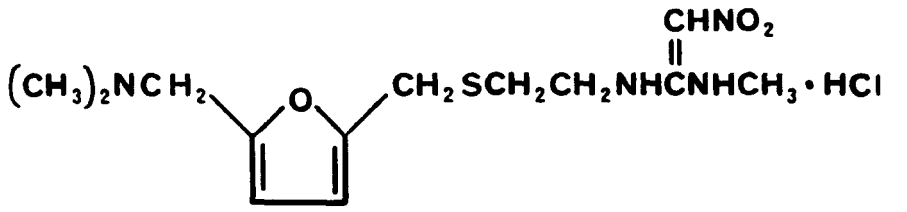

Figure 1 - Structure of ranitidine hydrochloride.

the column and did not try the method for the analysis of dosage forms. The maintenance of 40° temperature for columns is not very common. An HPLC method (2) to analyze ranitidine in total parenteral nutrient solution using a C_2 column has been reported. The details of this method were not reported. Another reported method (3) required the use of counterion (pentane sulfonic acid) for the analysis of ranitidine in parenteral nutrient solutions and I/V admixtures (4). The counterions are usually considered only when the drug is not retained on the column, since they can shorten the lives of costly columns.

The purpose the these investigations was to develop a stability indicating reverse-phase HPLC method without the use of a counterion to quantify ranitidine hydrochloride in pharmaceutical dosage forms.

MATERIALS AND METHODS

Chemicals and Reagents - All the chemicals and reagents were USP-NF or ACS quality and used without further purification. The dosage forms were of commercial lots.

Apparatus - The HPLC (5) was equipped with a multiple wavelength detector (6) and a recorder (7).

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TABLE 1

List of Various Mobile Phases Used

Number	Composition	pH (± 0.05)
1	17.5% V/V of acetonitrile and 0.02 M ammonium acetate in water.	6.8
2	17.5% V/V of acetonitrile and 0.01 M phosphate buffer in water.	6.4
3	10% V/V of methanol, 7% V/V acetonitrile and 0.01 M phosphate buffer in water.	5.8
4	As above	5.0

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Column - A nonpolar column (8), 30 cm x 3.9 mm i.d. was used.

Chromatographic Conditions - The various mobile phases used are presented in Table 1. The flow rate was 2.0 ml/min and the sensitivity was set at 0.04 AUFS (262 nm). The chart speed was 30.5 cm/hr and the temperature was ambient.

Stock and Standard Solutions of Ranitidine Hydrochloride - A 0.1% aqueous solution of ranitidine (from hydrochloride salt) was prepared using a simple solution method. A 0.1% solution of caffeine (the internal standard) in methanol was prepared using a simple solution method. These solutions were mixed and diluted further with water as needed. The most commonly used standard solution contained 60 µg/ml of free ranitidine base and 30 µg/ml of caffeine.

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Assay Solution from Injection (25.0 mg/ml) of Ranitidine - It was diluted with water to contain 60 µg/ml of ranitidine. Before diluting, enough of the stock solution of caffeine was added to contain 30 µg/ml.

Assay Solutions from Tablets (150 or 300 mg) - Ten tablets were ground to a fine powder. A quantity of the powder representing 150 mg of ranitidine was mixed with 2 drops of dilute sulfuric acid and 5 drops of water. After mixing thoroughly, the mixture was brought to volume (100.0 ml) with water and filtered (9). First 10-15 ml of the filtrate was rejected and then some collected for further dilution with water to contain 60 µg/ml of ranitidine based on the label claim. The stock solution of caffeine (the internal standard) was added before the diluting to contain 30 µg/ml.

Decomposed Solutions - A 3.0 ml quantity of the stock solution of ranitidine was mixed with either 1 ml of ∿1N H_2SO_4 or 1 ml of ∿1N NaOH and heated to boiling for 20 minutes using a hot plate. More water was added as needed. The solutions were cooled and neutralized by adding either 1 ml of ∿1N H_2SO_4 or 1 ml ∿1N NaOH. Each solution was brought to volume (50.0 ml) with water and assayed. A 3.0 ml quantity of the stock solution was mixed with 3.0 ml quantity of the hydrogen peroxide solution (3%) and stored at room temperature for 20 minutes. The mixture was then brought to volume (50.0 ml) with water and assayed.

Assay Procedure - A 20.0 µl quantity of the assay solution was injected into the chromatograph using the described conditions (mobile phase 3, Table 1). For comparison, an identical volume of the stan-

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dard solution containing identical quantity of ranitidine (based on the label claim) was injected after the assay solution eluted.

Calculations - Since preliminary investigations indicated that the ratio of the peak heights were related to the concentrations of ranitidine (range tested 30-72 µg/ml), the results were calculated using the following equation:

$$\frac{(R_{ph})_A}{(R_{ph})_S} \times 100 = \text{percent of the label claim found}$$

where $(R_{ph})_A$ is the ratio of peak heights of the drug to the internal standard in the assay solution and $(R_{ph})_S$ that of the standard solution.

RESULTS AND DISCUSSION

The results indicate (Table 2) that ranitidine hydrochloride can be assayed using the developed HPLC method. The method is accurate and precise with a percent relative standard deviation of 1.5 based on 5 readings. The recovery from the synthetic mixtures was quantitative (Table 2). The excipients present in the tablets and injection did not interfere with the assay procedure (Figure 2). When developing the assay procedure, first of all mobile phase 1 (Table 1) was used at 320 nm (the wavelength of maximum absorption). With this mobile phase at 320 nm, no suitable internal standard could be used due to lack of absorption at this high wavelength. Then the wavelength of 262 nm was used since ranitidine had good absorption at this wavelength and caffeine could be used as the internal standard. However, there were two new problems which needed to be resolved. One was the interference from phenol (the

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TABLE 2

Assay Results

Dosage Form	Claim Ranitidine per Tablet or per ml	Percent of the Label Claim Found
Tablets	150	99.8
Tablets (different lot)	150	100.4
Tablets (different lot)	150	100.9
Tablets	300 mg	99.5
Tablets (different lot)	300 mg	100.8
Injection	25 mg	99.9
Injection (different lot)	25 mg	100.7
Synthetic Mixtures		
150 mg ranitidine + 150 mg of lactose		99.7
100 mg ranitidine + 200 mg of lactose		99.7

preservative present in the injection) which had the same retention time as ranitidine. Phenol did not interfere at 320 nm since it did not have any absorption. The second problem was the retention time of caffeine, which was less than that of the drug. This was a problem since one of the products of decomposition (peak 4 in Figure 2) eluted out at the same time. Considering the facts that at lower pH values of the mobile phase, phenol (the weak acid) should be retain-

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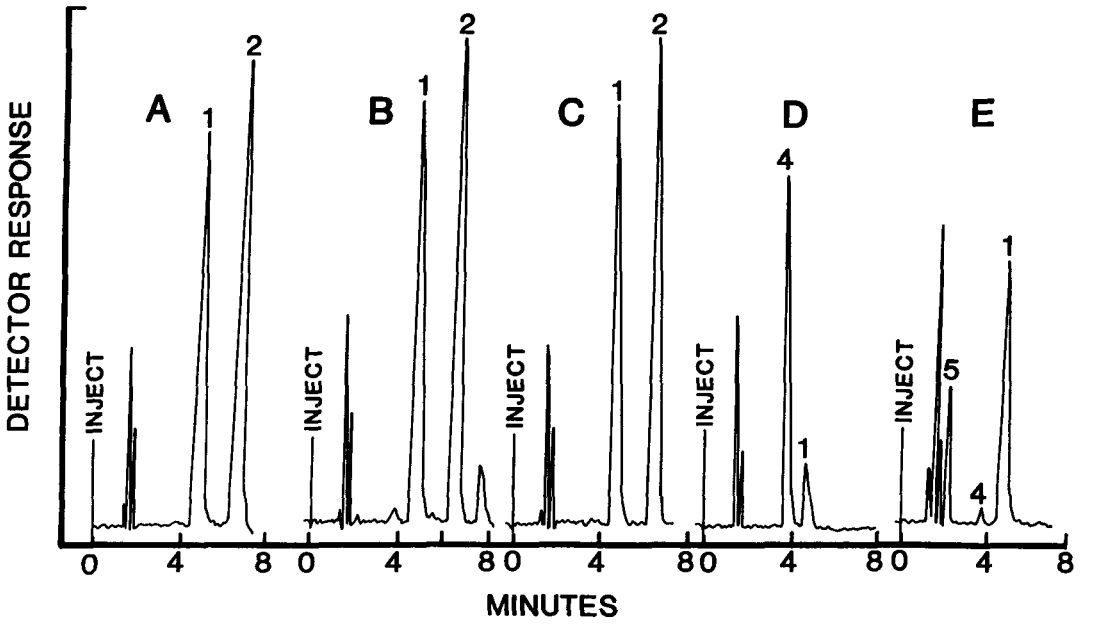

Figure 2 - Sample chromatograms. Peaks 1-3 are from ranitidine, caffeine (the internal standard) and phenol (the preservative added to the injection), respectively. Peaks 4-5 are from the unidentified products of decomposition. Chromatogram A is from a standard solution; B from the injection; C from the tablets; D from a decomposed sample (20 minutes boiling with sodium hydroxide- see text); and E from a decomposed sample (using hydrogen peroxide- see text). For chromatographic conditions, see text.

ed for a longer time on the nonpolar column and ranitidine (the weak base) for a shorter time, the problem could be resolved. Caffeine was not affected too much by the pH changes of the mobile phase since it is a neutral molecule. For example, when the pH of the mobile phase was reduced to 6.4 (mobile phase 2, Table 1), ranitidine separated from phenol but it was not quite a baseline separation. On reducing the pH to 5, the ranitidine was not retained on the column for too long and phenol had a long retention time. On

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reducing the strength of the organic solvent in the mobile phase at pH 5 (mobile phase 4, Table 1), the ranitidine had a retention time of 4 minutes and phenol about 9 minutes. Incidentally, in our experience 10% methanol equals approximately 5% of acetonitrile in terms of strength of the organic solvent in the mobile phase. At pH 5, with a lower strength of the organic solvent, the retention time of caffeine (the internal standard) increased so that it started eluting after the ranitidine with complete separation. At pH 5, there was a problem, one of the products of decomposition (peak 4 in Figure 2), was eluting at the same time as ranitidine. To resolve this, the pH of the mobile phase was increased to 5.8 (mobile phase 3 in Table 1) which increased the retention time of ranitidine without affecting the retention time of the product of decomposition. The separation with mobile phase 3 was complete (Figure 2D) and therefore, it was adopted for the assay procedure.

The sample which was decomposed using sulfuric acid lost about 15% of the potency and showed a small new peak in the chromatogram (same as #4 in Figure 2). However, 20 minute boiling with sodium hydroxide caused the sample to decompose by almost 84.4%. There was a new peak in the chromatogram (Figure 2D). On treatment with hydrogen peroxide at room temperature (see text), the loss in potency was 37.8% and the sample showed new peaks in the chromatogram (Figure 2E). Therefore, the method appears to be stability-indicating.

The extraction procedure for ranitidine hydrochlordie from tablets is very simple. The results were excellent (Table 2).

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REFERENCES

(1) P.E. Carey and L.E. Martin, J. Liq. Chromatography, 2, 1291 (1979).

(2) S.E. Walker and C.D. Bayliff, Am. J. Hosp. Pharm., 42, 590 (1985).

(3) L. Bullock, R.B. Parks, V. Lampasona and R.E. Mullins, Am. J. Hosp. Pharm., 42, 2683 (1985).

(4) V. Lampasona, R.E. Mullins and R.B. Parks, Am. J. Hosp. Pharm., 43, 921 (1986).

(5) ALC 202, Waters Associates, Milford, MA.

(6) Spectroflow monitor SF770, Kratos Inc., Ramsey, NJ.

(7) Omniscribe 5213-12, Houston Instruments, Austin, TX.

(8) Microbondapak C_{18} (theoretical plates 3000), Waters Associates, Milford, MA.

(9) Cat. #9-8035E, Fisher Scientific, Fairlawn, NJ.

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