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QUANTITATION OF NIZATIDINE IN CAPSULES USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A stability-indicating high-performance liquid chromatography method for the quantitation of nizatidine in capsules has been developed. The method is accurate and precise with a percent relative standard deviation of 0.34 based on 6 readings. A number of inactive ingredients present in the capsules did not interfere in the assay procedure. The recovery from the synthetic mixtures was quantitative. The extraction procedure from the capsules is very simple. The drug appears to be very sensitive to bases (such as sodium hydroxide) since 100% of the drug decomposed on boiling for 35 minutes. The drug was very stable when boiled with sulfuric acid.

BACKGROUND

Nizatidine (Figure 1) is the newer H_2 blocker which is used to treat gastric ulcers. It is available as capsules (150 and 300 mg). The drug is not official yet; therefore, no method for the quantitation of nizatidine in capsules has been recommended. High Performance Liquid Chromatography at low wavelength (228 - 230 nm) have been used (1, 2) to assay nizatidine in extemporaneously prepared solutions. At these low

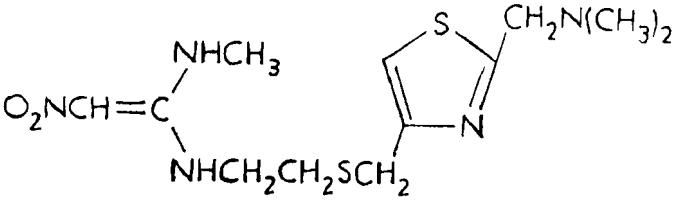

Figure 1 - Structure of Nizatidine.

wavelengths, the noise level is usually very high. The purpose of these investigations was to develop a stability-indicating high performance liquid chromatography method for quantitation of nizatidine in capsules.

MATERIALS AND METHODS

Chemical Reagents: All the chemicals and reagents were USP-NF or ACS quality and were used without further purification. Nizatidine was supplied by Eli Lilly & Co. and ranitidine was supplied by Glaxo Laboratories and used as received.

Apparatus: A high-pressure liquid chromatograph (Waters ALC 202) equipped with a universal injector (Rheodyne Model 7125), a multiple wavelength detector (Schoeffel's SF 770, Kratos, Inc.) and a recorder (Omniscribe 5213-12, Houston Instruments, Austin) was used. A micro C_{18} column (Waters Associates, 30 cm x 3.9 mm i.d.) was the stationary phase.

Chromatographic Conditions: The mobile phase contained 10% v/v of acetonitrile in 0.02M KH_2PO_4 aqueous buffer. The flow rate was 1.0 ml/min., the wavelength was 315 nm (sensitivity 0.1 AUFS), the chart speed was 30.5 cm/hr and the temperature was ambient.

Preparation of Stock and Standard Solutions: A stock solution of nizatidine was prepared fresh every day by dissolving 50.0 mg of the powder in enough water to make 100.0 ml of the solution. A stock

solution of ranitidine (the internal standard) was prepared by dissolving 40.0 mg of the powder in enough water to make 100.0 ml of the solution. A most commonly used standard solution was prepared by mixing 2.8 ml of the stock solution of drug with 3.5 ml of the stock solution of the internal standard, and bringing to volume (50.0 ml) with water. The solutions of other concentrations were prepared as needed.

Extraction from Capsules: Five capsules (each containing 150 or 300 mg of the drug) were weighed accurately, a portion of the powder representing 50 mg of nizatidine was triturated with 50 ml water for 5 minutes using a pestle and mortar. The mixture was brought to volume (100.0 ml) with water and filtered (Fisher's 9-803-SE filter paper), the first 10 ml of filtrate was rejected, and then collected for further dilution. A 2.8 ml quantity of the clear filtrate was mixed with 3.5 ml of the stock solution of ranitidine and brought to volume (50.0 ml) with water.

Decomposition of Nizatidine: A 3.5 ml of the stock solution of nizatidine (20 mg per 100 ml of water) was mixed with 15 ml of water and either ~ 1 ml of ~ 1N H_2SO_4 or 0.4 ml of ~ 2.5N NaOH in a 150 ml beaker. The mixture was heated to boiling (~ 35 minutes), cooled and brought to volume (25.0 ml) with water. Before bringing to volume, the pH values of the solutions were adjusted to weakly acidic. The mixtures were injected without the addition of an internal standard in order to detect new peaks (if any) in the chromatograms.

Assay Procedure: A 20 μl quantity of the assay solution was injected into the chromatograph using the conditions described. For comparison, an identical volume of the standard solution was injected after the sample eluted. The standard solution contained identical concentrations of the drug (based on the label claim) and the internal standard.

TABLE 1 ASSAY RESULTS

Name of the Sample	Percent of the Label Claim Found	Other Ingredients (if any)
Capsules 150 mg	98.0	gelatin, pregelatinized starch, silicone, starch, titanium dioxide, yellow iron oxide and magnesium stearate.
Capsules 150 mg (different lot)	99.0	as above
Capsules 300 mg	98.8	Instead of magnesium stearate, they contained carboxymethyl-cellulose sodium, povidone, red iron and talc.
Synthetic Mixture 1	100.2	50 mg drug in 200 mg of glucose
Synthetic Mixture 2	99.9	50 mg drug in 200 mg of lactose

Calculations: Preliminary investigations indicated that the ratio of peak heights were related to the concentrations of the drug. The results were calculated using a simple equation:

$$\frac{(Rph)_a}{(Rph)_s} \times 100 = \text{percent of the label claim found,}$$

where $(Rph)_a$ is the ratio of the peak heights of drug to internal standard in the assay solution and $(Rph)_s$ that of the standard solution.

RESULTS AND DISCUSSION

The results (Table 1) indicate that the developed method can be used to quantify nizatidine in the capsules. The method is accurate and precise with percent relative standard deviation of 0.34 based on 6 readings. The ratio of peak heights were related to the drug concentrations (range tested 8-48 μg/ml of nizatidine). The correlation factor, r was 0.999. The recovery from the synthetic mixtures was

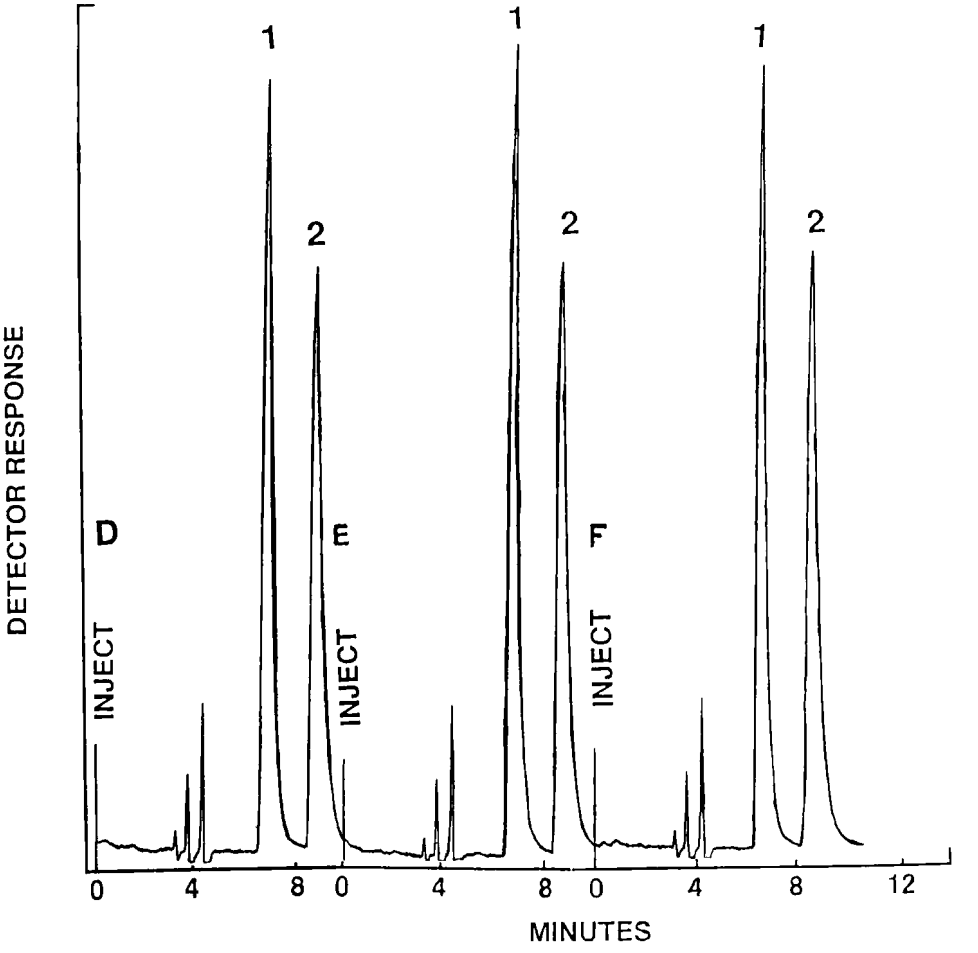

Figure 2 - Sample Chromatograms.

Peaks 1-2 are from nizatidine and ranitidine (the internal standard), respectively. Chromatogram D is from a synthetic mixture in lactose (Table 1), E from a synthetic mixture in glucose (Table 1) and F from 150 mg capsules (number 2 in Table 1). A chromatogram from a standard solution is presented in Figure 3C. For Chromatographic conditions, see text.

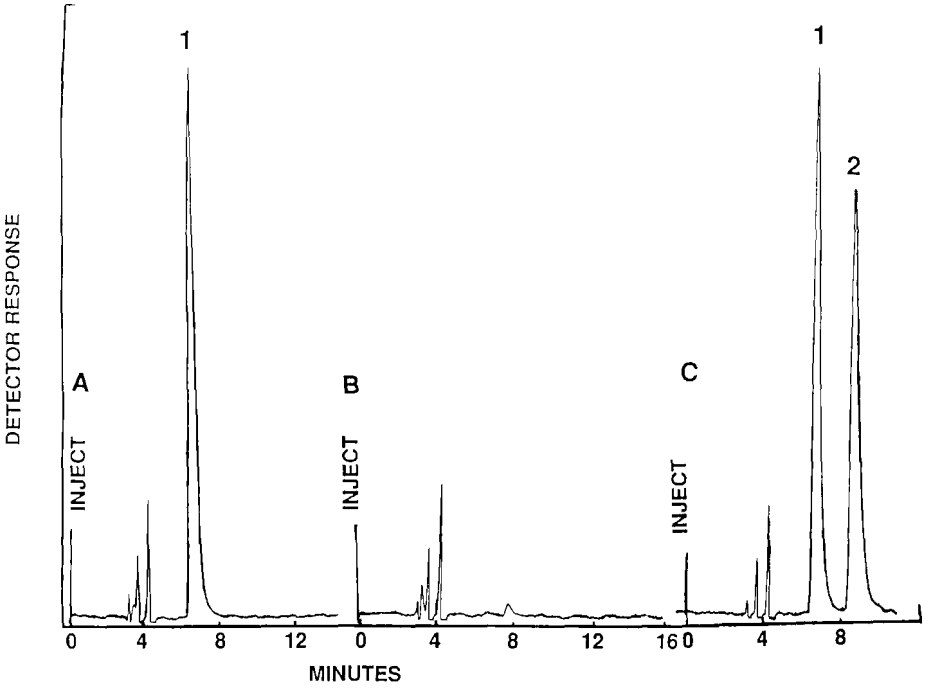

Figure 3 - Sample Chromatograms.
Peaks 1-2 are from nizatidine and ranitidine, respectively. Chromatogram A is from an acid decomposed solution; B from a base decomposed solution (no internal standard was added), and C from a standard solution. For Chromatographic conditions, see text.

quantitative (Table 1) and there was no interference (Figure 2) from the excipients present in capsules such as gelatin, pregelatinized starch, silicone, starch, titanium dioxide, yellow iron oxide, magnesium stearate, carboxymethylcellulose sodium, povidone, red iron oxide and talc. The procedure for the extraction of drug from the capsules is very simple. There was very little decomposition of the drug in the

solution decomposed by using acid (Figure 3A) and almost all the drug decomposed when sodium hydroxide was used (Figure 3B) for decomposition.

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