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QUANTITATION OF FAMOTIDINE IN PHARMACEUTICAL DOSAGE FORMS USING HIGH-PERFORMANCE LIQUID CHROMATOGRAPHY

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ABSTRACT

A stability-indicating high-performance liquid chromatography method for the quantitation of famotidine in injections, suspensions and tablets has been developed. The method is precise and accurate with a percent relative standard deviation of 1.1-1.3 based on 5 readings. The excipients present in the dosage forms did not interfere with the assay procedure. The recovery from the synthetic mixtures was quantitative. The samples decomposed under drastic conditions showed a total of 3 new peaks in the chromatograms.

BACKGROUND

Famotidine (Figure 1) is a new histamine H_2-receptor antagonist. It is being used extensively for the treatment of gastric ulcers. Famotidine is available in 3 dosage forms, injection, powder for suspension and tablets (20 and 40 mg). Famotidine is still not official in the USP-NF. There is very little information in the literature for its quantitation in pharmaceutical dosage forms. The purpose of these

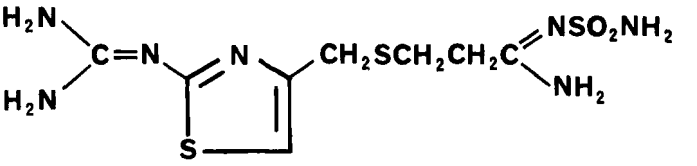

Figure 1 Structure of famotidine.

investigations was to develop a stability-indicating high-performance liquid chromatography method for the analysis of famotidine in pharmaceutical dosage forms.

MATERIALS AND METHODS

Reagents and Chemicals: All the reagents and chemicals were USP-NF or ACS quality and used as such. The famotidine powder (Merck Sharp & Dohme) was used without further purification. All the dosage forms analyzed were from the commercial lots.

Apparatus: A high-pressure liquid chromatograph (Waters ALC 202) equipped with a universal injector (Waters U6K), a multiple wavelength detector (Schoeffel's SF 770, Kratos Inc.) and a recorder (Omniscribe 5213-12, Houston Instruments) was used. A C_{18} column (Microbondapak, 30 cm x 3.9 mm i.d., Waters Associates) was the stationary phase.

Chromatographic Conditions: The mobile phase contained 12% V/V of methanol, 2% V/V of acetonitrile, 0.1% V/V of glacial acetic acid in 0.01M KH_2PO_4 aqueous buffer solution. The flow rate was 2.0 ml to 3.6 ml/min, the sensitivity was 0.04 AUFS (at 268 nm), the chart speed was 30.5 cm/hr and the temperature was ambient.

Preparation of Solutions: A 0.04% stock solution of famotidine in dimethylformamide was prepared fresh every week. A 0.07% stock solu-

tion of sulfamerazine (the internal standard) in methanol was prepared fresh every month. The stock solutions were mixed and diluted with water as needed. The most commonly used standard solution contained 40.0 µg/ml of famotidine and 28.0 µg/ml of sulfamerazine.

Extraction Procedure - From Injection: A 2.0 ml quantity of the injection (10.0 mg/ml) was diluted to 50.0 ml with dimethylformamide. A 2.5 ml quantity was mixed with 1.0 ml quantity of the stock solution of sulfamerazine and brought to volume (25.0 ml) with water.

From Powder for Suspension: The suspension was prepared according to the directions on the label. A 2.5 ml quantity of the suspension was diluted to 50.0 ml with dimethylformamide, filtered (Fisher's 9-803-5-E filter paper), first 15 ml of the filtrate was rejected and then collected for further dilution as given above under injection.

From Tablets: Ten tablets were accurately weighed and ground to a fine powder. A quantity of the powder representing 20.0 mg (based on the label claim) of famotidine was accurately weighed, mixed with 40 ml of dimethylformamide and the mixture stirred occasionally for about 5 minutes. It was then brought to volume (50.0 ml) with dimethylformamide, filtered, first 15 ml of filtrate was rejected and then collected for further dilution as given above under injection.

From 20 mg Tablets for Content Uniformity: One whole tablet was mixed with ∿35 ml of dimethylformamide in a 50 ml Erlenmyer flask, then sonicated (Brasonic Ultrasonic cleaner Model B-2200R-1) for 5 minutes and shaken mechanically (Forma's model 2564 Shaker Bath) for 60 minutes at a speed setting of 6 (on a scale of 0-10). The mixture was brought to volume (50.0 ml) with dimethylformamide, filtered, first 15 ml of the filtrate was rejected and then collected for further dilution as explained above under injection.

Decomposition of Famotidine Under Drastic Conditions: A 5.0 ml of the stock solution of famotidine was mixed with 15 ml of water and either ∿1 ml of ∿1N H_2SO_4 or 1 ml of ∿1N NaOH solution in a 150 ml beaker. The mixture was heated to boiling using a hot plate (more water was added as needed) for 10 minutes, cooled and neutralized using either 1N H_2SO_4 or 1N NaOH solution. A 5 ml quantity of dimethylformamide was added and the mixture brought to volume (50.0 ml) with water and assayed. No internal standard was added in order to detect additional peaks from the decomposition products.

Assay Procedure: A 20.0 µl quantity of the assay sample was injected into the chromatograph using the conditions described above. For comparison, an identical quantity of the standard solution was injected after the assay sample eluted. The standard solution contained identical concentrations of drug (based on the label claim) and the internal standard.

Calculations: Preliminary investigations indicated that the ratio of peak heights (famotidine/sulfamerazine) were directly related to concentrations of famotidine (range tested ± 40% of the standard concentration). Therefore, the results were calculated using a simple 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 the peak heights of the assay sample and $(R_{ph})_s$ that of the standard solution. In the case of decomposed solutions without internal standard, the results were estimated by the direct comparison of famotidine peak heights of the assay/standard and then multiplying by 100.

TABLE 1
ASSAY RESULTS OF VARIOUS DOSAGE FORMS AND SYNTHETIC MIXTURES

Dosage Form	Claim per Tablet or per ml (mg)	Percent of the Label Claim Found
Injection	10	101.2
Suspension	8	100.3
Tablets	20	93.8
Tablets (different lot)	20	99.7
Tablets	40	97.2
Tablets (different lot)	40	99.2
Synthetic Mixture #1	40 mg + 260 mg dextrose	99.7
Synthetic Mixture #2	40 mg + 260 mg lactose	99.9

RESULTS AND DISCUSSION

The results indicate (Tables 1-2) that the developed method can be used to quantify famotidine in pharmaceutical dosage forms. The method is accurate and precise with percent relative standard deviations (RSD) based on 5 readings of 1.1-1.3. The separation of the internal standard, sulfamerazine, from the drug, famotidine, was complete (Figure 2). The method is stability-indicating since the samples decomposed under drastic conditions showed new peaks in the chromatograms and lost most of potency (Figure 3C and D). For example, a sample decomposed using sulfuric acid showed only 9% of the famotidine left intact (Figure 3C) and a new peak (peak 2) in the chromatogram. A sample

TABLE 2
CONTENT UNIFORMITY RESULTS OF 20 mg TABLETS

Tablet #	Assay Results (% of the label claim)
1	97.9
2	98.4
3	97.4
4	97.0
5	102.0
6	97.2
7	99.6
8	99.9
9	96.8
10	96.0
Average = 98.2	
% RSD = 1.8	

decomposed using sodium hydroxide showed all of famotidine decomposed (Figure 3D) and 3 new peaks in the chromatogram.

Extraction Procedures from Injection and Suspension: The procedures were very simple and there was no interference from the various excipients present in these dosage forms. For example, injection also contained L-aspartic acid and mannitol. The suspension also contained citric acid, flavors, microcrystalline cellulose, carboxymethyl cellu-

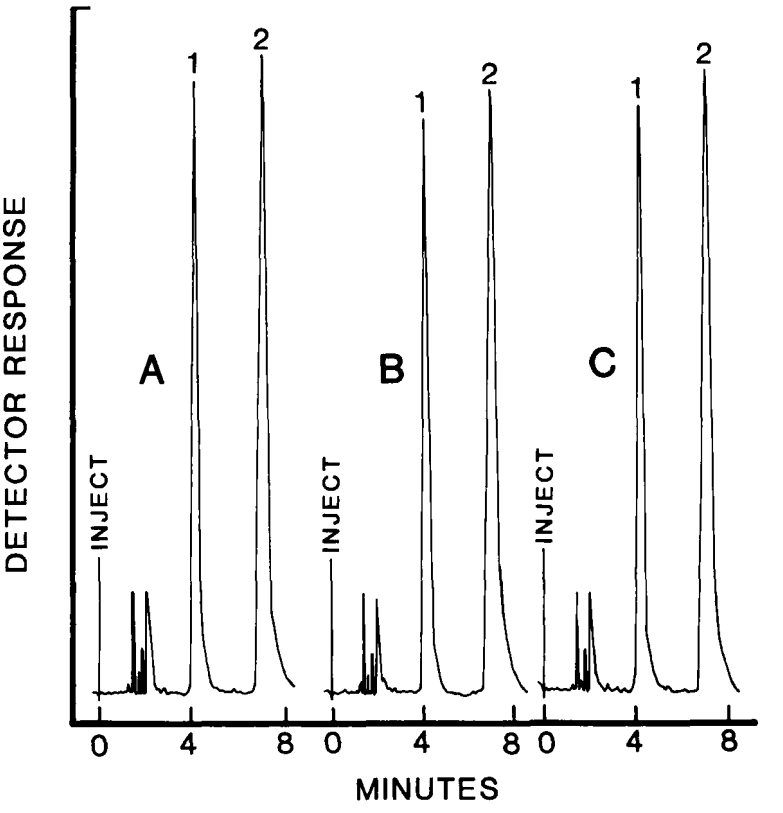

Figure 2 Sample chromatograms. Peaks 1-2 are from famotidine and sulfamerazine (the internal standard), respectively. Chromatogram A is from a standard solution, B from suspension and C from 40 mg tablets. For chromatographic conditions, see text. The flow rate was 3.6 ml/min.

lose sodium, sucrose, xanthan gum, and the preservatives, sodium benzoate, sodium methylparaben and sodium propylparaben.

Extraction Procedure from Tablets: To develop an appropriate procedure for the extraction of famotidine from tablets was most challenging in this project. The insert (1) provided by the manufacturer states that

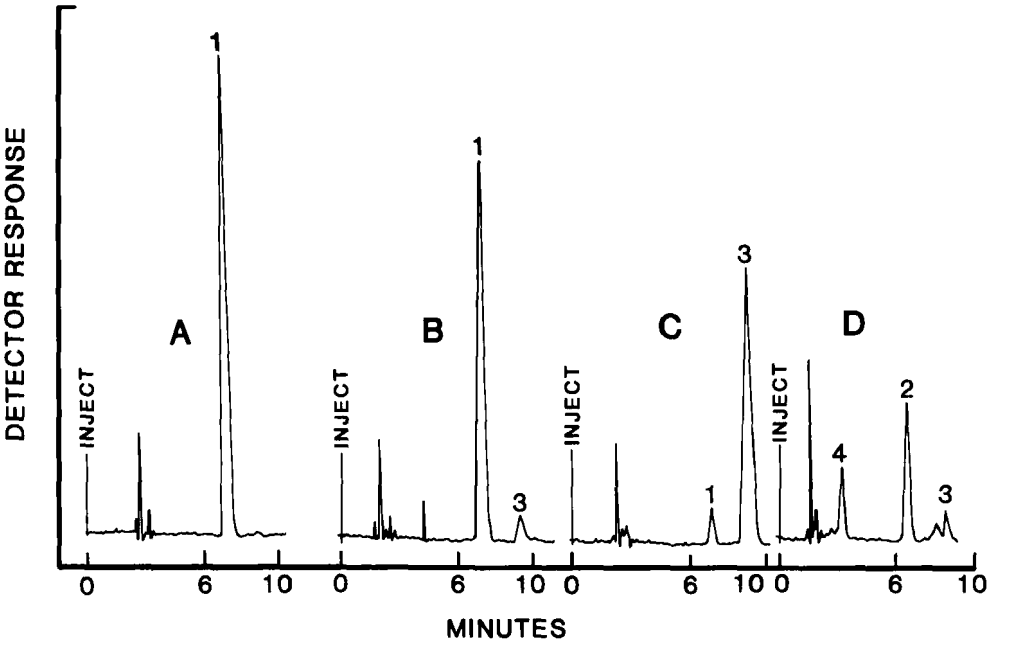

Figure 3 Sample chromatograms. Peak 1 is from famotidine and all the others are from the products of decomposition. Chromatogram A is from a standard solution; B from a 20 mg tablet when drug was extracted using sulfuric acid (see discussion); C from a sample decomposed using sulfuric acid, and D from a sample decomposed using sodium hydroxide (see text). For chromatographic conditions, see text. The flow rate was 2.0 ml/min.

famotidine is freely soluble in glacial acetic acid, slightly soluble in methanol, very slightly soluble in water and practically insoluble in ethanol.

Initially, the authors tried to extract the active ingredient using ∿2 ml of ∿1N H_2SO_4 per 40 mg of the powder and bringing the mixture to 100.0 ml with water. After filtering and diluting, the

assay results indicated only about 80% recovery (Figure 3B) and a new peak in the chromatogram (peak 2). This peak is typical of the decomposed drug in the acidic medium (Figure 3C). Even substituting glacial acetic acid for sulfuric acid did not produce quantitative recovery. The recovery of drug with 50% methanol was only about 65%. Later on, the manufacturer provided us with more physio-chemical data which indicated famotidine was freely soluble in dimethylformamide. Hence the extraction procedure given above (see materials and methods) was developed. For content uniformity, a different procedure (see text under materials and methods) was developed to prevent grinding of each tablet to a fine powder. The method gave quantitative results (Table 2). There was no interference from the various excipients present in the tablets. Tablets also contained hydroxypropyl methylcellulose, hydroxypropyl cellulose, iron oxides, magnesium stearate, microcrystalline cellulose, starch, talc and titanium dioxide. The recovery from the synthetic mixtures (Table 1) was quantitative.

REFERENCE

1. PEPCID® (Famotidine) insert, issued December 1986 (A.H.F.S. Category 56:40), Merck Sharp & Dohme, West Point, PA.