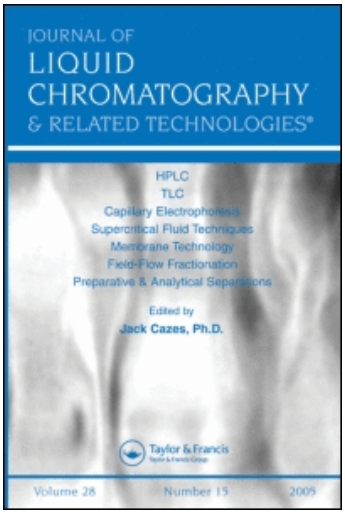

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Liquid Chromatographic Analysis and Degradation Kinetics of Famotidine

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LIQUID CHROMATOGRAPHIC ANALYSIS AND DEGRADATION KINETICS OF FAMOTIDINE

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ABSTRACT

A reverse phase HPLC method for the determination of famotidine in tablets has been developed. The method is stability indicative as exhibited by its ability to separate drug from its degradation products. Chromatography was performed with an octadecyl silane bonded silica column at ambient temperature using UV detection at 254 nm. The mobile phase consisting of methanol and 0.02 M sodium acetate (pH adjusted to 4.5) in the ratio of 1:4 was pumped at 1.0 ml per minute. A percent RSD of $< 0.86\%$ and correlation coefficient of 0.9993 were achieved over the concentration range studied (2-100 $\mu g.ml^{-1}$). This drug exhibits instability both in acidic and alkaline media. Kinetic study showed that degradation in acidic media follows an apparent first order process.

INTRODUCTION

Famotidine is a new H_2 antagonist and chemically it is propanimidomide, N'-(aminosulfonyl)-3-[[[2-[(diaminomethylene)

amino] 4-thiozolyl]-methyl] thio]. The drug and its tablet formulations are official in USP[1] XXII which specifies a nonaqueous titration for the assay of raw material and HPLC method for tablet analysis. The other methods reported in the literature for the analysis of the drug include colorimetry[2] and HPLC methods[3-5]. In this paper the development and validation of a new HPLC method for the quantification of famotidine in presence of its decomposition products are described. The method is simple, sensitive and rapid, and has been applied to investigate the degradation of famotidine.

EXPERIMENTAL

Chromatographic conditions :

The analysis were performed on a Shimadzu HPLC system LC-6A equipped with a variable wavelength detector SPD-6AV set at 254 nm and a Zorbax ODS column 25 cm x 4.6 mm (i.d.). The mobile phase consisting of methanol and 0.02M sodium acetate (pH adjusted to 4.5 with acetic acid) in the ratio of 1:4 was pumped at a flow rate of one ml/min. Sample injections were of 20 µl. For linearity study, varying amounts of stock solution of drug (500 $\mu g.ml^{-1}$, 0.2-10 ml) were pipetted out into a series of 50 ml volumetric flasks. The volume was made upto the mark with mobile phase. The solutions were injected in triplicate and the mean peak area were calculated and used for construction of the calibration graph.

Specificity of the method :

Five ml of stock solution containing 500 $\mu g.ml^{-1}$ of famotidine was mixed with 5 ml of 2N hydrochloric acid, 5 ml of 2N sodium hydroxide or 1 ml of 3% hydrogen peroxide solution in 50 ml volumetric flasks. The flasks were kept in constant temperature water bath at 65° ± 0.5°C for 30 min.

After cooling the pH was adjusted to 5.5 with 0.1N HCl or 0.1N NaOH and the volume was made upto the mark with water. Five ml solution was further diluted to 25 ml with mobile phase and analysed chromatographically.

Method for kinetic study :

Five ml of stock solution (500 $ug.ml^{-1}$) was mixed with either NaOH or HCl of appropriate concentration in 50 ml volumetric flasks. The flasks were kept in a constant temperature waterbath at 45°, 55° or 65° (± 0.5°C). Five ml solutions were sampled at appropriate time intervals. The reaction was quenched by cooling and neutralising with calculated amount of 0.1N HCl or 0.1N NaOH in 25 ml volumetric flasks. The volume was made upto the mark with mobile phase and solutions were used for HPLC analysis.

RESULTS AND DISCUSSION

Typical chromatograms recorded by injecting standard famotidine sample and famotidine solution treated with hydrochloric acid, sodium hydroxide and hydrogen peroxide at 65°C are given in Fig. 1. From these it is clear that famotidine exhibits instability in both acidic and alkaline media. This drug is also suscetible to oxidative degradation. One or more additional peaks appeared on the chromatograms due to the formation of degradation products which were not identified. However the peaks were well separated and hence the method is applicable to the selective determination of famotidine.

Tablet analysis :

The practicality of the method was demonstrated by the analysis of tablet formulations. For this purpose a calibration graph was constructed by plotting peak area versus concentration of famotidine. The plot was linear in the concentration

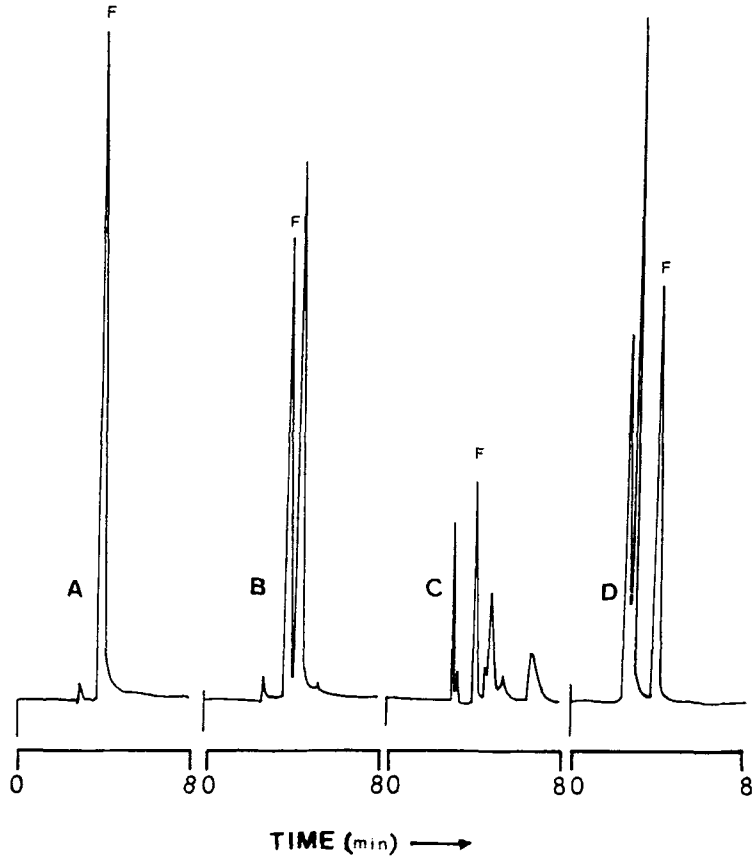

Fig. 1 : Chromatograms of Famotidine solution in **A.** Water **B.** 0.1N HCl **C.** 0.1N NaOH **D.** 0.5% H_2O_2 heated at 65°C for 30 min. (Peak F-Famotidine).

range 2-100 $\mu g.ml^{-1}$ with an intercept 0.0508. A correlation coefficient of 0.9993 and percent RSD of 0.86% were obtained. The limit of quantitation of famotidine was 2 $\mu g.ml^{-1}$ under the operating conditions employed. By using this calibration graph and the dilution factor the content of famotidine in tablet was calculated. The results are given in Table 1.

TABLE - 1, Results of famotidine tablet analysis

Lot	Labelled amount mg/tablet	Found mg/tablet	% Recovery	RSD %
A	20	19.56	97.80	0.64
B	20	19.73	98.65	0.82
C	40	39.82	99.55	1.14
D	40	39.34	98.35	0.96

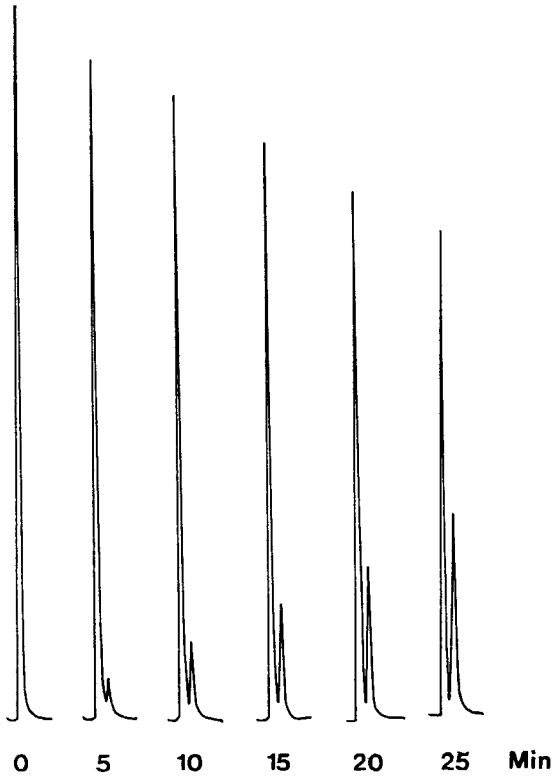

Fig. 2 : Chromatograms of Famotidine degradation as a function of time.

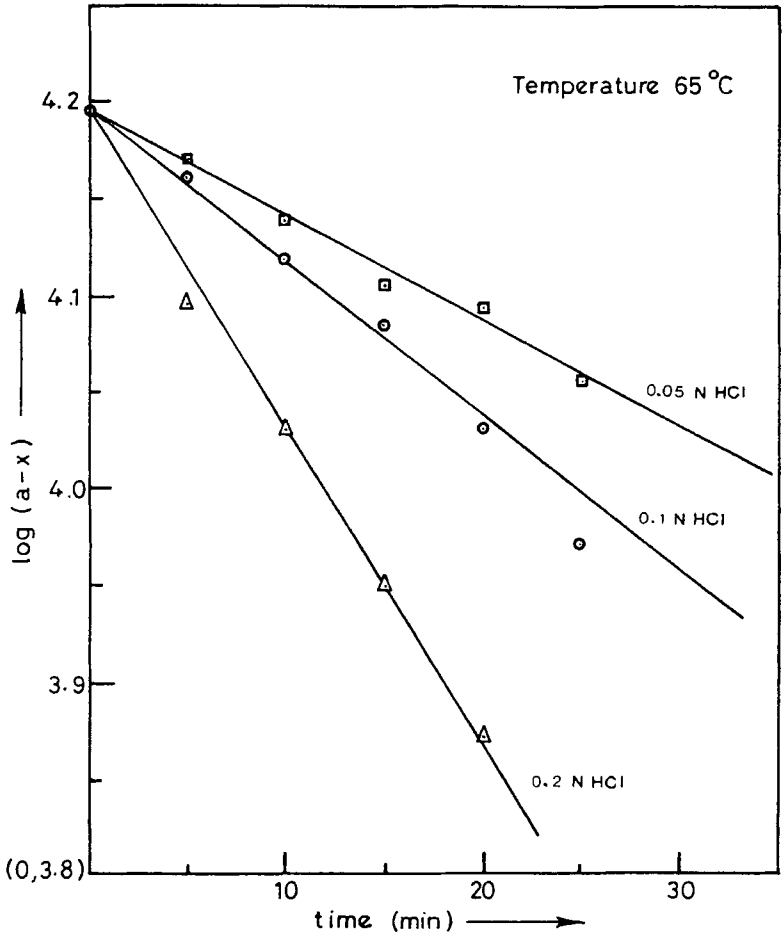

Fig. 3 : Pseudo-first order kinetic plots of Famotidine degradation.

Common excipients found in the tablet formulation did not interfere. Percent RSD for a single sample was < 1.2%. The present method is thus simple, selective and accurate for the determination of famotidine in tablets.

Degradation kinetics :

The method was found suitable to follow the kinetics of degradation of famotidine in acidic solutions. Samples withdrawn at various time intervals from the reaction mixture were quenched and analysed. Typical chromatograms so recorded are shown in Fig. 2. Changes in concentration computed from such chromatograms followed pseudo first order kinetics under the conditions employed (Fig. 3). Investigation into the effect of temperature on the reaction showed that Arrhenius equation was not strictly obeyed. This is possibly due to the changes in the mechanism of degradation reaction with temperature as evident from the appearance of different number of peaks on the chromatograms recorded at different temperatures.

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