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Kinetics of the acid-catalyzed hydrolysis of famotidine

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Summary

The kinetics of hydrolysis of famotidine were studied in 0.01–0.10 M hydrochloric acid solutions of 2 mg/ml using a stability-indicating high-performance liquid chromatographic assay with ultraviolet detection. The hydrolysis followed pseudo-first order kinetics with respect to famotidine concentration. The observed rate constant was found to depend on hydrogen ion concentration and was not influenced by the ionic strength. The specific hydrogen ion catalytic rate constant was calculated to be 3.427 $M^{-1} \cdot h^{-1}$ at 37 °C. The temperature dependence of famotidine hydrolysis was investigated in 0.1 M hydrochloric acid solutions having an ionic strength of 0.2 in the temperature range 37–55 °C. The activation energy was determined to be 63.7 kJ/mol. The impact of the acid-catalyzed hydrolysis on the stability of famotidine in the stomach was discussed. It was estimated that in the gastric pH 1–2 and with a gastric emptying half-life of 50 min in normal young adults about 5.3–35.8% of an oral dose of famotidine would undergo degradation in the stomach. This percentage might be even increased to 12.0–57.8% in the elderly.

Introduction

Famotidine is a new H_2-receptor antagonist of potent acid inhibitory effect and relatively low drug interaction potential (Krishna and Klotz, 1988). Further it has a longer duration of action than any of the older H_2-receptor antagonists (Koch, 1986). The drug is available as tablets of 20 and 40 mg and as vials for injection containing 20 mg famotidine.

Screening of the literature has revealed that kinetic studies on famotidine are lacking. Vincek (1985) reported on the stability of famotidine in biological fluids. The drug was found to lose 20% of the original concentration after storage in plasma at −15 °C for 1 year and 10–15% after storage in urine at 22–25 °C for 4 h. Biffar and Mazzo (1986) used 3 potential degradates of famotidine provided by Merck Sharp and Dohme Research Laboratories to characterize a high-performance liquid chromatographic assay. No details were presented on the identity of these products or how they were obtained. Yanagisawa et al. (1987) reported that famotidine was relatively susceptible to acid-catalyzed hydrolysis. The drug was shown to hydrolyze to a sulfamoyl amide in the presence of excess hydrochloric acid and to a carboxylic acid at elevated temperatures. The degradation products were found to have only weak

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antagonistic potency. More recently, Guvener and Ates (1988) investigated the stability of famotidine in simulated gastric medium. The drug was found to lose about 34% of the original concentration in 1 h and about 88% in 3 h.

The objective of this work was to investigate the kinetics of degradation of famotidine in acidic solutions of varying pH. Knowledge about the acid stability was utilized to assess the extent of possible degradation of the drug in the stomach after oral administration and its impact on bioavailability.

Materials and Methods

Materials

A sample of famotidine was kindly provided by Dar Al Dawa Development and Investment Co. Ltd., Na'ur, Jordan. Ammonium acetate, salicylic acid (internal standard), hydrochloric acid and glacial acetic acid were analytical grade. Acetonitrile was HPLC grade. Potassium chloride (used to adjust ionic strength) was reagent grade. Distilled water from an all-glass still was used to prepare the buffers.

Test solutions

Standardized solutions of hydrochloric acid (0.01, 0.05 and 0.10 M) at fixed ionic strength ($\mu = 0.2$) were prepared. The solutions were placed in a thermostatically controlled water bath maintained at $37 \pm 0.5\,^{\circ}C$. To test the effect of ionic strength on the rate of decomposition of famotidine, standardized solutions of hydrochloric acid (0.1 M) with various total ionic strengths ($\mu = 0.1$, 0.2, 0.3 and 0.5) were prepared. To study the effect of temperature on the rate of degradation of famotidine, standardized hydrochloric acid solutions (0.1 M) and constant ionic strength ($\mu = 0.2$) were prepared. The solutions were incubated at 37, 45 and $55\,^{\circ}C$.

Apparatus

The high-performance liquid chromatograph used was composed of a Waters model 501 pump, a Waters model U6K universal liquid injector and a Waters model 481 variable wavelength detector. A column (25 cm × 4.6 mm i.d.) packed with Spherisorb ODS (5 μm particles) (Phase Separations, Queensferry, U.K.) was used. The chromatograms were recorded with a JJ CR452 chart recorder (J.J. Lloyd Instruments Ltd., Southampton, U.K.).

Analytical method

Famotidine was determined by a stability-indicating HPLC method (Suleiman et al., 1988). In this method, solutions of the drug were eluted with a mobile phase consisting of a mixture of 84% ammonium acetate buffer and 16% acetonitrile (pH 2.9). The flow rate was 2.0 ml/min and the effluent was monitored spectrophotometrically at 254 nm. Quantitation of the drug was achieved with reference to a suitably constructed calibration curve using the peak height ratios of drug to internal standard.

Kinetic studies

The reactions were initiated in all cases by dissolving a weighed quantity of famotidine in the preheated hydrochloric acid solution to give an initial concentration of 2 mg/ml. Aliquots were withdrawn at appropriate time intervals and analyzed for the drug using the HPLC method described above. Residual famotidine concentrations were plotted against the corresponding times on semilogarithmic graph paper. The observed rate constants were calculated from the slopes of the linear plots by statistical regression ($r > 0.98$).

Results and Discussion

The stability-indicating characteristic of the HPLC assay is demonstrated in Fig. 1. A typical chromatogram of the drug (I) and the internal standard (II) is shown in Fig. 1a. Chromatograms of degraded solutions of famotidine are presented in Fig. 1b–d. At 1 h, the chromatogram shows 3 peaks: II ($r_t = 3.5$ min), I ($r_t = 6.0$ min) and one degradation product, III ($r_t = 8.5$ min) (Fig. 1b). At 24 h (Fig. 1c) and 150 h (Fig. 1d), the chromatograms show an additional peak, IV ($r_t = 15.75$ min). These results coincided with those obtained by thin-layer chromatography. Thin-layer chro-

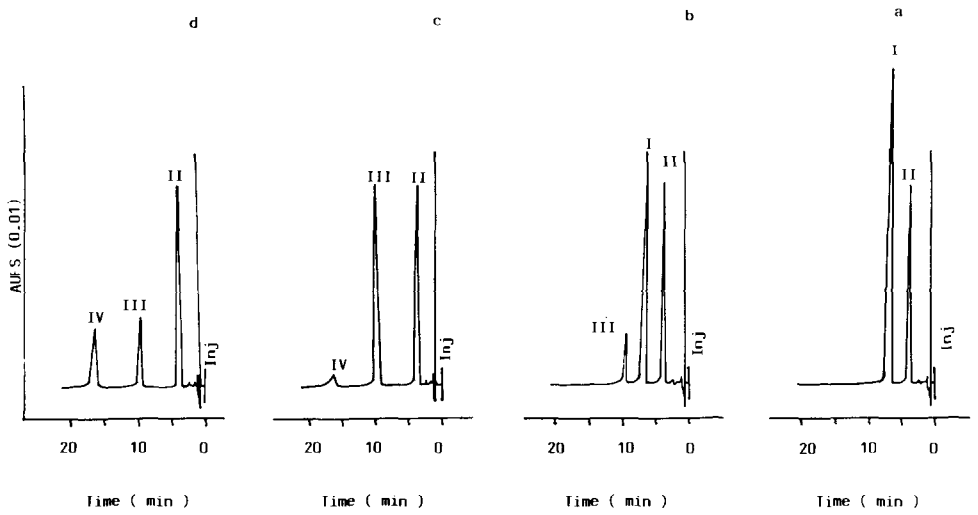
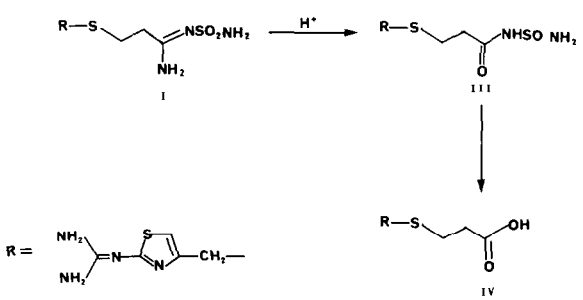


Fig. 1. HPLC chromatograms of famotidine in 0.1 M HCl ($\mu = 0.2$) at 37 °C. a: 0 h; b: 1 h; c: 24 h; d: 150 h. Chromatographic conditions: flow rate 2 ml/min; chart speed 2 mm/min; detector response 0.01 AUFS; detection wavelength 254 nm.

matograms of degraded solutions of famotidine developed in the solvent system (butanol–water–acetic acid, 4 : 2 : 1) showed 2 spots (corresponding to I and III) at 1 h and 3 spots (corresponding to I, III and IV) at 24 and 150 h, when visualized with iodine vapour.

A comparison of the chromatograms presented in Fig. 1c, d shows that the intensity of peak IV was increased at 150 h whereas that of peak III was decreased. This indicates that the degradation product (IV) was formed as a result of hydrolysis of III and not as a result of direct hydrolysis of I. This suggests that the decomposition of famotidine in hydrochloric acid solutions may occur according to the following scheme:

Typical plots for the decomposition of famotidine in hydrochloric acid solutions are illustrated



Scheme 1.

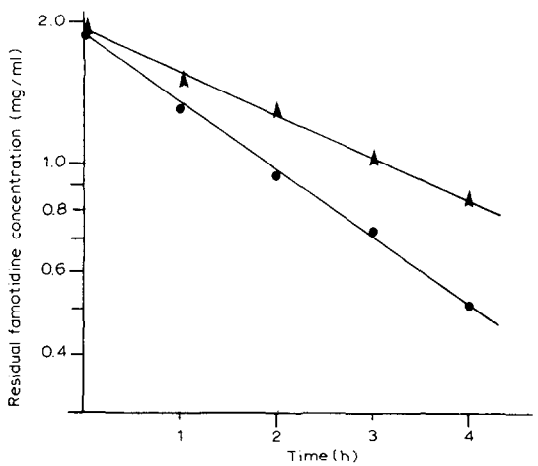


Fig. 2. First-order plots for the decomposition of famotidine at 37 °C and $\mu = 0.2$. ●, 0.01 M HCl; ▲, 0.05 M HCl.

TABLE 1

Effect of pH on the observed pseudo-first order rate constant (K_{obs}) and the specific acid-catalyzed rate constant (K_H) at 37 °C ($\mu = 0.2$)

H^+ (M)	pH	K_{obs} (h^{-1})	K_H ($M^{-1}\ h^{-1}$)
0.01	2.13	0.040	4.000
0.05	1.47	0.201	4.010
0.10	1.03	0.322	3.220
			$\bar{x} = 3.427$

TABLE 2

Effect of ionic strength on the hydrolysis of famotidine (0.1 M HCl, 37 °C)

Ionic strength	K_{obs} (h^{-1})
0.1	0.302
0.2	0.322
0.3	0.315
0.5	0.311

in Fig. 2. It is obvious that the hydrolysis followed an overall pseudo-first order kinetics with respect to famotidine. The observed pseudo-first order rate constants (K_{obs}) were found to be directly proportional to the hydrogen ion concentration as shown in Table 1. Thus the kinetic results obtained can be described as follows:

$$-\frac{d(I)}{dt} = K_{obs}(I)$$

Where $K_{obs} = K_H(H^+)$ and K_H is the second-order rate constant for specific acid-catalyzed hydrolysis. At 37 °C and $\mu = 0.2$, K_{obs} was calculated to be 3.427 $M^{-1} \cdot h^{-1}$.

The ionic strength was found not to have any significant influence on the rate of hydrolysis of famotidine in 0.1 M hydrochloric acid solutions at values up to $\mu = 0.5$ (Table 2).

The effect of temperature on the rate of hydrolysis of famotidine is shown in Table 3. A plot of the data according to Arrhenius equation gave a straight line. An activation energy of 63.7 kJ/mol was calculated from the slope of this line.

To assess the significance of the acid-catalyzed hydrolysis of famotidine on the stability of the drug in the stomach after oral administration, important factors such as gastric acidity and the gastric emptying rate must be considered. The normal gastric pH is within the range 1–2 and the mean gastric emptying half-time is 50 min (range 21–132 min) in normal young adults (mean age 26 years) and 123 min (range 67–454 min) in elderly people (mean age 77 years) (Evans et al., 1981). Using the relationship

$$\log(H) = 0.13 - pH$$

which is valid at 37 °C and $\mu = 0.2$ (Harned and Hamer, 1933) and the mean value of 3.427 $M^{-1} \cdot h^{-1}$ for K_H, the K_{obs} at pH 1, 1.5 and 2 were calculated to be 0.462, 0.146 and 0.0462 h^{-1}, respectively. If the gastric emptying process is assumed to be associated with a first-order rate constant (K_{ge}) of 0.83 h (derived from a $t_{1/2}$ value of 50 min), the percentage of famotidine which may survive the acid-catalyzed decomposition in the stomach can be calculated from the equation for two simultaneous first-order processes:

$$\% \text{ undecomposed famotidine} = \frac{K_{ge}}{K_{ge} + K_{obs}} \times 100$$

The values calculated were 64.2, 85.0 and 94.7% for pH 1, 1.5 and 2, respectively. Thus, the acid-catalyzed hydrolytic decomposition in the stomach of orally administered famotidine may contribute to its lower bioavailability (the mean oral bioavailability was 37% (Compoli-Richards and Clissold, 1986)). However, other factors such as the relatively high polarity of the drug may have a role. Other processes such as enzymatic hydrolysis in the gastric and intestinal mucosa cannot be ruled out.

The impact of the acid-catalyzed degradation of famotidine in the stomach would be more significant in elderly patients who have a prolonged gastric emptying half-time (123 min). In these patients about 12.0–57.8% of the drug would undergo decomposition in the stomach, thus lowering the amount of intact drug available for absorption. The reduced gastric acidity encountered in the elderly (incidence of achlorhydria in aged people over 62 years is more than 20% (Vanzant et al., 1932)) would also contribute to lowering the oral

TABLE 3

Effect of temperature on the hydrolysis of famotidine (0.1 M HCl, $\mu = 0.2$)

Temperature (°C)	K_{obs} (h^{-1})
37	0.322
45	0.529
55	1.129

bioavailability of famotidine solid dosage forms due to an adverse effect on the dissolution rate of the basic drug (Mayersohn, 1986).

In conclusion, famotidine was found to undergo acid-catalyzed hydrolysis in hydrochloric acid solutions of varying pH. The hydrolytic-degradation in the gastric fluid (pH 1–2) was established to be significant, particularly in the elderly. Enteric coating of the drug may provide protection in the environment of the stomach. Research is undergoing in our laboratory to evaluate the in vivo availability of the drug from an experimental enteric-coated tablet formulation.

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