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Solubility, Stability and Ionization Behaviour of Famotidine

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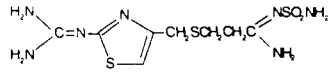
Abstract—The pK_a of famotidine was determined at 23 ± 0.2°C to be 6·76, 6·98 and 6·89 by a spectrophotometric, solubility, and partitioning method, respectively. The pH-solubility profile of famotidine indicated an intrinsic solubility of 2·7 mM at 23°C. Degradation of famotidine followed pseudo-first-order kinetics over a pH range of 1–11 at 37 ± 0.2°C and at an ionic strength (μ) of 0·5. The pH-rate profile was accounted for by the specific acid and base catalysed reactions as well as water-catalysed decomposition of both protonated and free famotidine. A pK_a of 6·60, determined by potentiometry at 37 ± 0.5°C ($\mu = 0.5$), was used in the kinetic calculations. Maximum stability occurred at pH 6·3. Undissociated acetic acid, dihydrogen phosphate ion and glycine anion were found to contribute to the general acid and base catalyses. pH-dependency of the apparent octanol-water partition coefficient of famotidine indicated a partition coefficient of 0·23 for free famotidine at 23 ± 0.2°C.

Famotidine is a potent inhibitor of histamine H_2 receptors; it suppresses both the acid concentration and volume of gastric secretion in man (Heinrich 1986). On an equimolar basis, it is reported to be about 7·5 and 20 times more potent than ranitidine and cimetidine, respectively, in inhibiting basal and pentagastrin-stimulated gastric acid secretion (Dammann et al 1983).



Although famotidine reportedly undergoes minimal first-pass metabolism, its oral bioavailability in man has been reported to be low and variable, ranging from 20 to 66% (Campoli-Richards & Clissold 1986; Kroemer & Klotz 1987). High polarity and gastric degradation are believed to contribute to its low bioavailability (Suleiman et al 1989; Kraus et al 1990).

Famotidine is not available as an oral solution. This fact, coupled with the inadequate stability of its available liquid dosage forms prompted us to develop and evaluate a 10 mg mL^{-1} solution of famotidine which would be stable at 25°C for at least two years. A survey of the literature reveals inadequate and incomplete information about the physicochemical characteristics of famotidine. The pK_a of famotidine has been reported to be 7·1 at 25°C (Gerald 1992), 6·45 at 37°C (Najib & Suleiman 1990) and 6·7 (no temperature indicated) (Vincek et al 1985), none of which are reported to be determined by an accurate and reproducible method such as spectrophotometry or potentiometry. Also, the ionic conditions under which they were determined have not been reported. Reports pertaining to the solution stability of famotidine are limited to its degradation in plasma and urine (Vincek et al 1985), parenteral nutrient solutions (Das Gupta et al 1988) and acidic media (Guvener & Ates 1988; Suleiman et al 1989).

To aid in the development of a famotidine solution, its relevant physicochemical properties needed to be determined. Therefore, the objectives of this study were to determine the pK_a by a spectrophotometric method, generate a pH-solubility and a pH-stability profile, assess the contribution of buffers to the degradation, and investigate the pH-dependency of the apparent octanol/water partition coefficient.

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Materials and Methods

Materials

Famotidine and sulfamerazine (internal standard) were purchased from Sigma Chemical Co., St Louis, MO, USA. Standardized HCl and NaOH were received from Fisher Scientific Co., Fair Lawn, NJ, USA. Buffer substances and solvents were of reagent and HPLC grade, respectively. Distilled, deionized water was used to prepare buffer solutions.

Analytical methods

The HPLC assay has been described earlier (Islam & Narurkar 1991). Spectral measurements were carried out on a Response UV-VIS spectrophotometer (Gilford systems, Oberlin, OH, USA). Buffers used in the stability study included: at pH < 3, HCl; at pH 3·5–5·2, acetate; at pH 6–8, phosphate; and at pH 9–10·25, glycine. A constant ionic strength of 0·5 was maintained by using appropriate amounts of KCl.

Determination of pK_a by spectrophotometry

Due to limited aqueous solubility of famotidine at 23°C, spectrophotometry was chosen for the determination of pK_a. The method described by Albert & Serjeant (1984) was used with a 0·2 mM famotidine solution. From the UV spectra of the protonated and free (molecular) forms of famotidine (at pH 2·04 in 0·01 M HCl and pH 10·7 in 0·01 M glycine buffer, respectively) an analytical wavelength of 291·5 nm was obtained. Individual pK_a values were determined using seven

phosphate buffer solutions, ranging from pH 6 to 7·3 (μ=0·03) and employing the equation:

$$pK_a = pH + \log\frac{A_M - A}{A - A_I} \quad (1)$$

where A_M is the absorbance of the molecular species, A_I is the absorbance of the ionized (protonated) species, and A is the total absorbance. The thermodynamic pK_a (pK_a^T) of famotidine was calculated using the equation (Albert & Serjeant 1984):

$$pK_a^T = pK_a - \frac{0{\cdot}51\mu^{1/2}}{1 + 1{\cdot}5\mu^{1/2}} \quad (2)$$

Determination of pH-solubility profile

Excess famotidine was added to 3 mL deionized water in a Teflon-lined, screw-capped scintillation vial. Variable volumes of either HCl or NaOH were added to adjust the pH and the vial was shaken horizontally in a shaker (Eberbach Corporation, Ann Arbor, MI, USA) for 24 h (sufficient for equilibration) at 23±0·2°C. The suspension was passed through a 0·2 μm membrane filter (Alltech Assoc., Deerfield, IL, USA) with the initial portion discarded to ensure filter saturation. An aliquot of the filtrate was diluted and analysed by HPLC, while the rest of the filtrate was used for pH determination (Chemcadet Digital pH-meter, Cole-Parmer Instrument Co., Oberlin, OH, USA).

Kinetic studies

Degradation kinetics of famotidine were examined at 37±0·2°C (μ=0·5) over the pH range 1–11. Studies were initiated by adding 0·5 mL of a 2 mM stock solution of famotidine in methanol to 9·5 mL of previously equilibrated buffer in a thermostated water bath. Periodically withdrawn aliquots were analysed by HPLC either immediately or after thawing the frozen samples. No significant change in pH was observed during the experiment. Buffer catalytic effect was examined by varying only the buffer concentration at a particular pH, the pH being within the effective range of the buffer. All determinations were done in duplicate.

pK_a determination for kinetic studies

pK_a of famotidine at 37±0·5°C (μ=0·5) was determined by the potentiometric method (Albert & Serjeant 1984). Increased aqueous solubility of famotidine at 37°C allowed the use of this method. Fifty millilitres of a 4 mM solution of famotidine was prepared in CO_2-free water and was transferred to a 100 mL beaker placed on a heating mantle attached to a Powerstat variable autotransformer (The Superior Electric Co., Bristol, CT, USA), which was set at 37°C. The solution was then titrated with 20 μL increments of 1 M HCl with constant stirring and under a slow stream of N_2. A pH meter with an ATC probe (Orion Research Inc., Model 811, Boston, MA, USA), calibrated to ±0·002 pH units with pH 7·0 and 4·0 buffers, was used to monitor the pH. An average pK_a was calculated from eight determinations.

Determination of partition coefficient

The partitioning of famotidine between mutually presaturated *n*-octanol and buffer at pH 2–10 and 23±0·2°C was examined by measuring the concentration of famotidine in the aqueous phase at equilibrium. Two hours provided adequate time for equilibration while minimizing degradation. The pH-dependency of the partition coefficient of famotidine was evaluated by the equation (Hasegawa et al 1984):

$$P_{app} = P_m - \frac{[H_3O^+]P_{app}}{K_a} \quad (3)$$

where P_{app} is the apparent (observed) partition coefficient of famotidine, P_m is the partition coefficient of the free form and K_a is the ionization constant. Two determinations were made at end pH.

Results and Discussion

pK_a determinations

The reported pK_a values of famotidine have not been determined by an accurate and reproducible method and do not provide the ionic conditions under which they were determined. In our study, pK_a of famotidine at 23°C (μ=0·03) from the spectrophotometric method was determined to be 6·76±0·025 (n=7) which when converted by equation 2 gave a thermodynamic pK_a (pK_a^T) of 6·69. These values differ from the reported value of 7·1 (at 25°C). However, as noted earlier, there is no report as to how the pK_a of 7·1 was measured and whether it is thermodynamic.

pK_a of famotidine at 37°C (μ=0·5) was needed for our kinetic calculations, and was found by direct potentiometric titration to be 6·60±0·018 (n=8). This agrees well with the fact that the pK_a of a basic compound is expected to decrease with an increase in temperature (Albert & Serjeant 1984). The value of 6·60 closely matches the calculated value of 6·59 when the spectrophotometric pK_a (6·76) is adjusted for temperature and ionic strength.

Therefore, our results are in agreement with the observation by Newton et al (1982) that ionization constants are known to vary with the method used for their determination.

pH-solubility profile

Buffers were not used in the pH-solubility study because preliminary studies in our laboratory indicated significant changes in pH during the process of solubilization and an underestimation of saturation solubility at a particular pH. This is probably because of the inability of the buffers to maintain a constant pH and a salting-out effect caused by the presence of buffer salts.

The total solubility (S_t) of famotidine can be described by the following equation:

$$S_t = S_o + S_o[H_3O^+]/K_a \quad (4)$$

where S_o is the intrinsic solubility of famotidine. A plot of S_t vs $[H_3O^+]$ at 23°C was linear (r=0·97) as shown in Fig. 1 with an intercept (S_o) of 2·7 mM and yielded a K_a of $1{\cdot}04 \times 10^{-7}$ (pK_a=6·98) when the intercept was divided by the slope.

Degradation kinetics

The degradation of famotidine in aqueous solution at 37°C (μ=0·5) followed pseudo-first-order kinetics over the pH range 1–11. The observed rate constant for the overall

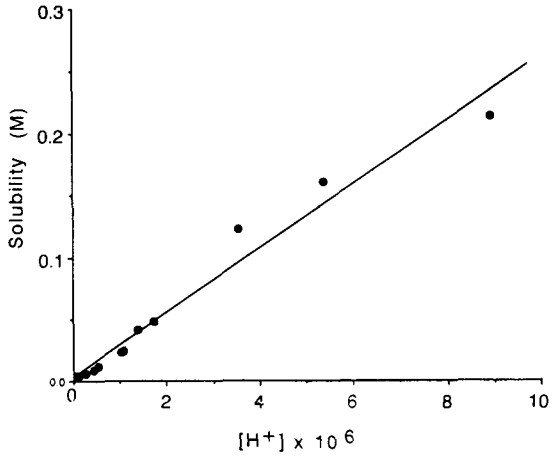

FIG. 1. Solubility vs hydrogen ion concentration plot for famotidine at 23±0·2°C according to equation 4.

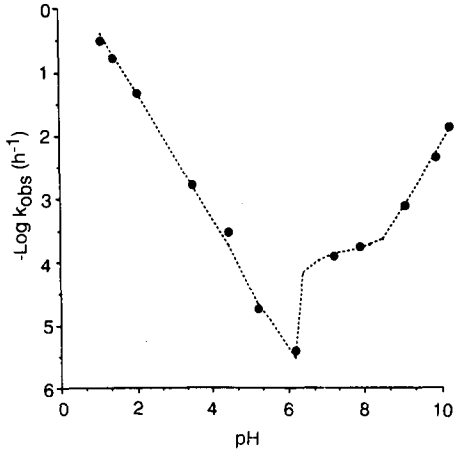

FIG. 2. pH-rate profile for famotidine degradation in aqueous solution at 37±0·2°C (μ=0·5). The data points are experimental and the line is theoretical, calculated by employing equation 7.

degradation of famotidine (k_{obs}) was calculated from the slopes of the straight lines obtained by plotting the logarithm of percent remaining vs time. The degradation products in highly acidic and alkaline media have been postulated earlier (Yanagisawa et al 1987; Suleiman et al 1989; Parasrampuria & Das Gupta 1989). Therefore, no attempt was made to characterize the degradation products in this study.

pH-rate profile

The pH-rate profile for the degradation of famotidine at 37±0·2°C (μ=0·5) is shown in Fig. 2. Maximum stability occurred at pH 6·3. In the pH range studied, famotidine exists as the free base (B) and in a protonated form (BH^+). Based on the shape of the pH-rate profile, the following reactions seem to contribute to the overall degradation (see Fig. 3).

The rate of overall degradation of famotidine can be expressed as:

$$\text{Rate} = k_{obs}[FAM]_t \quad (5)$$

Reaction				Rate constant
BH^+	+	H^+	---> Products	k_1
BH^+	+	H_2O	---> Products	k_2
BH	+	H_2O	---> Products	k_3
B	+	OH^-	---> Products	k_4

FIG. 3. Reactions contributing to the overall degradation of famotidine.

where $[FAM]_t$ is the total concentration of famotidine

and

$$k_{obs} = k_1 f_{[BH^+]}[H^+] + k_2' f_{[BH^+]}[H_2O] + k_3' f_{[B]}[H_2O] + k_4 f_{[B]}[OH^-]$$

$$= k_1 f_{[BH^+]}[H^+] + k_2 f_{[BH^+]} + k_3 f_{[B]} + k_4 f_{[B]}[OH^-] \quad (6)$$

where $k_2 = k_2'[H_2O]$, $k_3 = k_3'[H_2O]$.

It should be noted that k_1 and k_4 are second order and k_2 and k_3 are pseudo-first-order rate constants. Substituting for the fraction terms, the final expression for k_{obs} becomes:

$$k_{obs} = \frac{k_1[H^+]^2}{[H^+]+K_a} + \frac{k_2[H^+]}{[H^+]+K_a} + \frac{k_3 K_a}{[H^+]+K_a} + \frac{k_4 K_a[OH^-]}{[H^+]+K_a} \quad (7)$$

At pH less than 4, famotidine exists entirely in the protonated form ($f_{[BH^+]}=1$) with H^+ being the exclusive catalyst (reaction 1). Therefore, only the first term in equation 6 becomes important. Thus,

$$k_{obs} = k_1[H^+] \quad (8)$$

and

$$\log k_{obs} = \log k_1 + \log [H^+] \quad (9)$$

According to Harned & Hamer (1933) and Fort & Mitra (1990), $[H^+]$ and $[OH^-]$ concentrations in highly acidic and basic solutions at 37°C (μ=0·5) can be calculated using equations 10 and 11, respectively:

$$\log[H^+] = 0{\cdot}14 - \text{pH} \quad (10)$$

$$\log[OH^-] = \text{pH} - 13{\cdot}48 \quad (11)$$

Therefore, equation 9 becomes:

$$\log k_{obs} = \log k_1 + 0{\cdot}14 - \text{pH} \quad (12)$$

Using equation 12 up to pH 3·5, an average value of $k_1 = 3{\cdot}43$ $M^{-1}\ h^{-1}$ was calculated. This value agrees well with the average K_{H^+} value reported by Suleiman et al (1989) for degradation of famotidine in acidic media at 37°C (μ=0·2). The slope of the linear portion at pH < 3·5 in Fig. 2 was calculated to be −0·96, indicating specific acid catalysis.

From pH 4 to about 6·2, reactions 1 and 2 should govern the degradation of famotidine. Therefore, in this region,

$$k_{obs} = k_1 f_{[BH^+]}[H^+] + k_2 f_{[BH^+]} \quad (13)$$

k_2 was calculated to be $2{\cdot}48 \times 10^{-6}\ h^{-1}$ from the intersection of the linear regression plots ascribed to specific acid (pH < 4) and specific base (pH > 9) catalysis (Tu et al 1990).

At pH ≈ pK_a of famotidine, the shoulder-type break in the profile can be attributed to the higher reactivity of the free base to water, relative to that of the protonated base. Within a pH range 6·2–8, k_{obs} can be defined as:

$$k_{obs} = k_2 f_{[BH^+]} + k_3 f_{[B]} \quad (14)$$

Using a pK_a of 6·60 (at 37°C and $\mu = 0{\cdot}5$), the magnitude of k_3 at pH 7·22 and 7·92 was calculated from equation 14 and averaged to yield a value of $1{\cdot}69 \times 10^{-4}$ h^{-1}.

At pH > 9, the slope of the linear portion in Fig. 2 was 1·03, indicating specific base catalysis. Since, famotidine exists entirely in the free form in this region, with OH^- being the exclusive catalyst (reaction 4), equation 6 reduces to:

$$k_{obs} = k_4[OH^-] \quad (15)$$

and

$$\log k_{obs} = \log k_4 + \log [OH^-] \quad (16)$$

From equations 11 and 16,

$$\log k_{obs} = \log k_4 + pH - 13{\cdot}48 \quad (17)$$

An average value of $k_4 = 20{\cdot}30$ M^{-1} h^{-1} was obtained from the k_{obs} values at pH values of 9·07, 9·88 and 10·25. Thus, in basic media, the rate of degradation of famotidine is about 6 times faster than that in the acidic media. By employing simplified versions of equation 7 at different pH ranges, an excellent fit of the experimental data to the theoretical curve was obtained as shown in Fig. 2.

General acid-base catalysis

The decomposition of famotidine was found to be catalysed by all buffers used in this study. In such cases, k_{obs} is expressed as:

$$k_{obs} = k_o + k_{buff}[buffer] \quad (18)$$

where k_o is the pseudo-first-order rate constant corresponding to the non-buffer catalysed degradation and k_{buff} is the second order buffer catalytic rate constant. A plot based on equation 18 is linear as shown in Fig. 4 for the glycine system.

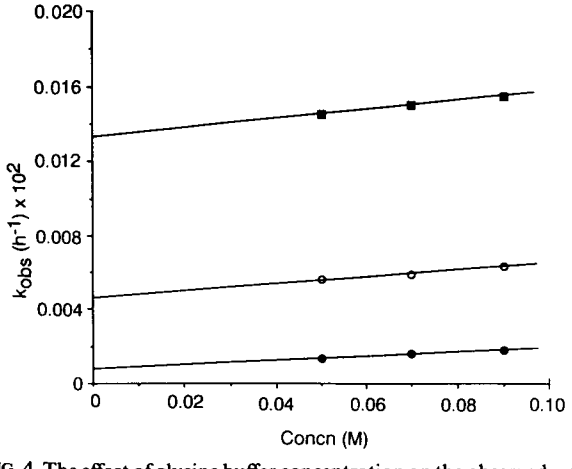

FIG. 4. The effect of glycine buffer concentration on the observed rate constant for the degradation of famotidine (37°C, $\mu = 0{\cdot}5$). ● pH 9·07, ○ pH 9·88, ■ pH 10·25.

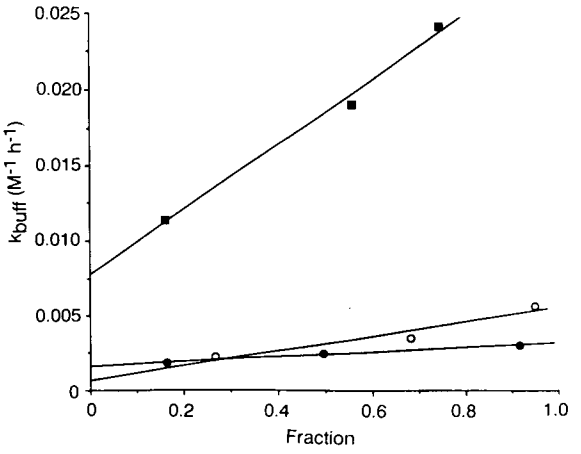

FIG. 5. Dependence of the apparent second-order rate constant for the buffer-catalysed degradation of famotidine at 37°C ($\mu = 0{\cdot}5$) on the fraction of catalysing buffer species. ● $H_2PO_4^-$, ○ CH_3COOH, ■ $NH_2CH_2COO^-$.

The buffer catalytic effect is seen to increase with an increase in pH in Fig. 4, suggesting glycine anion to be the predominant catalyst. The catalytic effect of phosphate (pH 6·17–7·92) and acetate (pH 3·5–5·2) buffers on the degradation of famotidine was also assessed by treating the rate data in a manner analogous to that used for the glycine system. Slopes (k_{buff}) of all these linear plots when plotted against the fractions of the predominant catalysing buffer species, are shown in Fig. 5. It appears that the magnitude of the catalytic effect of acetic acid and dihydrogen phosphate ion are not significant, relative to that of glycine anion. The catalytic constant $k_{CH_3COO^-}$ for example, for the acetate system was found to be $6{\cdot}70 \times 10^{-4}$ M^{-1} h^{-1} (when f_{CH_3COOH} was zero) and k_{CH_3COOH} to be $5{\cdot}56 \times 10^{-3}$ M^{-1} h^{-1} (when f_{CH_3COOH} was unity). Catalytic constants for the phosphate and glycine systems were: $k_{H_2PO_4^-} = 3{\cdot}17 \times 10^{-3}$ M^{-1} h^{-1}, $k_{HPO_4^{2-}} = 1{\cdot}6 \times 10^{-3}$ M^{-1} h^{-1} and $k_{NH_2CH_2COO^-} = 2{\cdot}92 \times 10^{-2}$ M^{-1} h^{-1}, $k_{NH_3 + CH_2COO^-} = 7{\cdot}69 \times 10^{-3}$ M^{-1} h^{-1}. Therefore, glycine anion was found to be the most catalytic buffer species in this study.

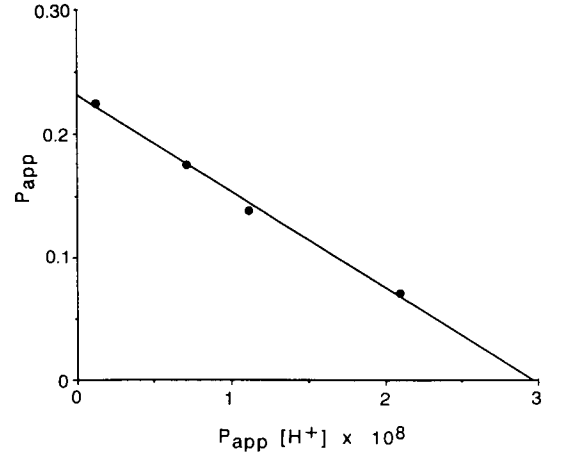

FIG. 6. Plot of the octanol/water partitioning data of famotidine at 23 ± 0·2°C according to equation 3.

Partition coefficient

The partition coefficient of famotidine remained low in acidic media, then increased with an increase in pH and reached a maximum value when famotidine was present entirely in the free form. Fig. 6 is a plot of the partitioning data according to equation 3. From this plot, a value of $1{\cdot}28 \times 10^{-7}$ for K_a ($pK_a = 6{\cdot}89$) from the slope and a value of 0·23 for P_m from the intercept were found. The partitioning data at pH 6·5–8·3 were used to construct Fig. 6, since the apparent partition coefficient was highly sensitive to pH in this region. Famotidine has a very low P_m, which is not surprising on the basis of its chemical structure. The molecule has four terminal primary amino groups, which in the nonprotonated state, can readily form H-bonds with water molecules and this could hinder its easy partitioning in the non-polar phase.

In conclusion, we have determined the pK_a of famotidine at 23°C by a reliable and accurate method such as spectrophotometry. We have also reported a thermodynamic pK_a for famotidine. The results of this study indicate that poor lipophilicity, poor aqueous solubility and susceptibility to gastric degradation may contribute to the low and variable oral bioavailability of famotidine.

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