Kinetic Spectrophotometric Determination of Famotidine in Commercial Dosage Forms

Nafisur RAHMAN[†] and Mohammad KASHIF

Analytical Research Division, Department of Chemistry, Aligarh Muslim University,
Aligarh (U.P.) 202002, India

A simple kinetic spectrophotometric method is described for the determination of famotidine. The method is based on the oxidation of the drug with alkaline potassium permanganate. The reaction is followed spectrometrically by measuring the rate of change of the absorbance at 610 nm. The initial-rate and fixed-time (at 12 min) methods are adopted for determining the drug concentration. The calibration graphs are linear in the ranges of 2 – 10 $\mu\text{g mL}^{-1}$ and 1 – 8 $\mu\text{g mL}^{-1}$ using the initial-rate and fixed-time methods, respectively. The method has been applied to the determination of famotidine in tablet formulations. The obtained results are compared statistically with those given by a reference spectrophotometric method.

(Received March 10, 2003; Accepted March 25, 2003)

Introduction

Famotidine, 3-[2-(diaminomethyleneamino)thiazol-4-ylmethylthio]-*N*-sulfamoylpropionamide, is a histamine H_2 receptor antagonist, with actions and uses similar to those of cimetidine. It is widely used in the management of gastrointestinal disorders, such as aspiration syndrome, dyspepsia, gastro-esophageal reflux disease, peptic ulcer and Zollinger-Ellison syndrome.¹

This drug is listed in United States pharmacopoeia,² which recommends non-aqueous titration and HPLC methods for its assay in bulk and tablet formulations, respectively.

UV-visible spectrophotometry is still considered to be a very convenient and low-cost technique, and hence is widely used for the determination of pharmaceuticals in bulk and dosage forms. A review of the literature revealed that charge-transfer complexation reactions between famotidine and π acceptors, such as 1,4-benzoquinone,³ chloranil, dichlorodicyanobenzoquinone, dichloronitrophenol⁴ and *p*-chloranilic acid,⁵ have been recommended for its determination in commercial tablet formulations. Extractive spectrophotometric methods⁶ have also been discussed which involve dichloromethane extractable 1:1 ion pair complex between famotidine and each of Bromocresol Green (BCG) and Bromothymol Blue (BTB). Beer's law was obeyed over the concentration ranges of 2.0 – 23.6 and 0.7 – 8.1 $\mu\text{g mL}^{-1}$ with molar absorptivities of 5.0×10^3 and $1.2 \times 10^4 \text{ L mol}^{-1} \text{ cm}^{-1}$ for famotidine-BCG and famotidine-BTB, respectively. The famotidine content was determined based on a reaction with sodium nitroprusside and measuring the absorbance at 498 nm.⁷ The difference spectrophotometric and quadratic polynomial coefficient methods⁸ have been cited in the literature for the determination of famotidine in pharmaceutical preparations.

A number of other techniques, such as HPLC,^{9–14} reversed-

phase HPLC,¹⁵ HPTLC¹⁶ and differential pulse voltammetry,¹⁷ and potentiometric titration,¹⁸ have been reported for the assay of famotidine in commercial dosage forms. Several manipulation steps are involved in some of these methods, which are not simple for the routine analysis of dosage forms.

The present communication describes a kinetically based spectrophotometric method for the determination of famotidine in pharmaceutical formulations. The method involves oxidation of the drug with alkaline potassium permanganate at room temperature and a subsequent measurement of the absorbance at 610 nm. The initial-rate and fixed-time methods are adopted after a full investigation.

Experimental

Apparatus

Spectronic 20 D⁺ Spectrophotometer (Milton Roy, USA) was used to measure the absorbance.

Materials and reagents

Famotidine was kindly provided by Wockhardt Ltd., India, and was used as received. Pharmaceutical preparations of famotidine, such as Topcid (Torrent Pharmaceuticals Ltd.), Famocid (Sun Pharmaceutical Industries Ltd.), Famotin (USV Ltd.) and Facid (Intas Labs Pvt. Ltd.), were purchased from local market. All other reagents used were of analytical grade.

A standard solution of famotidine (1 mg mL^{-1}) was prepared by dissolving 100 mg in 0.5 mL of 1 M NaOH, and further diluted to 100 mL with doubly distilled water. A working solution of famotidine (0.1 mg mL^{-1}) was prepared by the dilution of 2.5 mL of the standard solution to 25 mL with doubly distilled water. Aqueous solutions of sodium hydroxide (1 M) and potassium permanganate (0.01 M) were prepared in doubly distilled water.

Procedure for determination

Initial-rate method. Aliquots of 0.01 M KMnO_4 solution (1.0

[†] To whom correspondence should be addressed.
E-mail: cht17nr@yahoo.co.in

Fig. 1 Effect of the volume of 0.01 M KMnO_4 on the intensity of the color produced during the reaction (famotidine $10 \mu\text{g mL}^{-1}$; 1.5 mL of 1 M NaOH).

Fig. 2 Effect of the volume of 1 M NaOH on the intensity of color produced during the reaction (famotidine $10 \mu\text{g mL}^{-1}$; 1.0 mL of 0.01 M KMnO_4).

mL) and 1 M NaOH solution (1.5 mL) were transferred into a 10 mL volumetric flask. An accurate volume of the working solution of famotidine (0.2 – 1.0 mL) was added and diluted to volume with doubly distilled water. The contents of the mixture were shaken well and immediately transferred to a spectrophotometric cell. The absorbance was recorded as a function of time at 610 nm against a reagent blank at room temperature. The initial rate of the reaction at different concentrations was obtained from the slope of the tangent to the absorbance time curve.

A calibration graph was constructed by plotting the logarithm of the initial rate of the reaction vs. the logarithm of the molar concentration of famotidine. In the second procedure, the absorbance measured at a fixed time of 12 min was plotted against the final concentration of famotidine. The content of the drug was calculated either from the calibration graphs or regression equations.

Procedure for the determination of famotidine in pharmaceutical formulations. Ten tablets were accurately weighed and powdered. A portion equivalent to 50 mg of famotidine was extracted with methanol by shaking and filtered on Whatman No. 42 filter paper. The filtrate and washings were evaporated to dryness. The residue was dissolved in a minimum volume of 1 M NaOH and diluted according to need. The assay of famotidine was completed by the following recommended procedures.

Results and Discussion

In an alkaline medium, potassium permanganate oxidizes famotidine, resulting in the formation of manganate ion, which showed an absorption peak at 610 nm. Because the intensity of the color increased with time, a kinetically based method was elaborated for the determination of famotidine in dosage forms. The various experimental parameters affecting the formation of the reaction product were optimized.

Effect of the KMnO_4 concentration

To study the effect of the KMnO_4 concentration, aliquots of famotidine containing $100 \mu\text{g mL}^{-1}$ were transferred into a series of 10 mL volumetric flasks, followed by varying volumes of 0.01 M KMnO_4 (0.1 – 1.0 mL) and 1.5 mL of 1 M NaOH solutions. The absorbance at 610 nm was measured at a fixed time of 16 min. It is apparent from Fig. 1 that the absorbance increased with increasing volume of the KMnO_4 solution, and became constant at 0.8 mL. Thus, the adoption of 1.0 mL of

Fig. 3 Determination of the molar ratio between famotidine and KMnO_4 by the limiting logarithmic method. (●) Constant KMnO_4 concentration and variable famotidine concentration. (○) Constant famotidine concentration and variable KMnO_4 concentration.

0.01 M KMnO_4 in the final solution proved to be adequate for the maximum concentration of famotidine used in the calibration curve.

Effect of the NaOH concentration

The influence of the NaOH concentration on the formation of MnO_4^{2-} was examined critically. It was observed (Fig. 2) that the maximum absorbance of the reactant solution was obtained with 1.2 mL of 1 M NaOH. Hence, an optimum value of 1.5 mL was used throughout the experiment.

Stoichiometry

The combining ratio between potassium permanganate and famotidine was established by limiting the logarithmic method¹⁹ using two sets of experiments. In the first set, the famotidine concentration was varied while keeping a constant KMnO_4 concentration; in the second set, the KMnO_4 concentration was varied while keeping a constant concentration of famotidine. The logarithms of the absorbance were plotted against the logarithms of the varied concentration (Fig. 3). The combining molar ratio was obtained from the slope of the curves, and was found to be 1:1 famotidine/ KMnO_4 .

The famotidine contains a thio ether linkage which has an ability to oxidize to the corresponding sulfoxide. Based on literature background and our experimental findings, the reaction mechanism is proposed and given in Scheme 1.

Table 1 Calibration equations, precision and accuracy at different fixed times for famotidine concentrations in the range of 1 – 8 $\mu\text{g mL}^{-1}$

Parameter	Fixed time methods			
	4 min	8 min	12 min	16 min
Calibration equation	$A = 0.0124 + 0.0640C$	$A = 0.0166 + 0.0668C$	$A = 0.0044 + 0.0626C$	$A = 0.0137 + 0.0701C$
$\pm tS_a$	0.0146	0.0146	0.0137	0.01972
$\pm tS_b$	0.0029	0.0029	0.0027	0.0039
Molar absorptivity ($\text{l mol}^{-1} \text{cm}^{-1}$)	2.176×10^4	2.285×10^4	2.249×10^4	2.366×10^4
Correlation coefficient	0.9984	0.9986	0.9986	0.9977
Detection limit ($\mu\text{g mL}^{-1}$)	0.26	0.25	0.25	0.32
Variance	8.771×10^{-5}	8.633×10^{-5}	7.657×10^{-5}	1.580×10^{-4}
% RSD	1.19	1.33	1.20	1.25
SAE	0.0389	0.0433	0.0393	0.0409

$\pm tS_a$ = Confidence limit for intercept. $\pm tS_b$ = Confidence limit for slope. SAE = Standard analytical error.

Scheme 1

Fig. 4 Absorbance vs. time graph for the reaction between famotidine and KMnO_4 , showing the dependence of the reaction on famotidine concentration. (●) $5.92 \times 10^{-6} \text{ M}$; (○) $1.77 \times 10^{-5} \text{ M}$ and (▼) $2.96 \times 10^{-5} \text{ M}$.

Initial-rate method

The initial rates of the reaction were determined by measuring the slopes of the initial tangents to the absorbance time curves (Fig. 4). The order with respect to permanganate was estimated by studying the reaction at different initial concentrations of KMnO_4 with a fixed famotidine concentration. A plot of the initial rate, dA/dt , against the initial absorbance was linear while passing through the origin. This indicated that the order of the reaction with respect to permanganate at the start was one. The order with respect to famotidine was obtained by plotting the log initial rate of the reaction vs. the log molar concentration of famotidine, and was found to be unity.

Under the optimized conditions, the concentration of famotidine was determined using an excess of a KMnO_4 and NaOH solution with respect to the initial concentration of famotidine. As a consequence, a pseudo zero-order condition was obtained with respect to their concentrations. However, the initial rate of the reaction would follow a pseudo first-order equation,

$$\text{Rate} = \Delta A / \Delta t = K' C^n,$$

where C is the concentration of famotidine. The above equation is transformed into logarithmic equation as

$$\log(\text{rate}) = \log \Delta A / \Delta t = \log K' + n \log C.$$

A regression of the log rate versus log C gave a regression equation,

$$\log(\text{rate}) = 3.212 + 1.021 \times \log C,$$

with a correlation coefficient (r) of 0.9971.

The regression equation also confirmed that the reaction is first order with respect to the famotidine concentration. The calibration curve was found to be linear over the range 2 – 10 $\mu\text{g mL}^{-1}$. The confidence limit for the intercept value at the 95% confidence level was calculated using the relation $a \pm tS_{a,20}$ and was found to be 3.212 ± 0.0387 , which pointed towards a high reproducibility of the method. The detection limit,²¹ percent relative standard deviation, standard analytical error and variance were found to be 1.68%, 0.0319, and 3.76×10^{-4} , respectively. The small value of the variance confirmed the negligible scattering of the calibration data points around the line of the regression.

Fixed-time method

At a preselected fixed time, the absorbance of a green-colored solution containing varying amounts of famotidine was measured at 610 nm. Calibration graphs were constructed by plotting the absorbance against the initial concentration of famotidine at a fixed time of 4, 8, 12 and 16 min. The calibration equations, correlation coefficient, detection limit, variance and molar absorptivity are given in Table 1. It was observed that the most acceptable values of the relative standard deviation and the intercept were obtained at a fixed time of 12 min, and therefore were considered to be the most suitable time interval for measurements under this condition. The calibration graph was linear over the concentration range of 1 – 8 $\mu\text{g mL}^{-1}$.

A strong correlation also existed between the slope and the

Fig. 5 Joint confidence region for the slope and intercept of the line of regression at 12 min.

Table 2 Determination of famotidine in pharmaceutical preparations by the initial-rate method using the standard addition technique

Formulation ^a	Amount added/ $\mu\text{g mL}^{-1}$	Amount taken/ $\mu\text{g mL}^{-1}$	Total amount found/ $\mu\text{g mL}^{-1}$	Recovery, %	SAE ^b	RSD, %
Topcid 40	2	2	4.01	100.40	0.0199	1.21
	4	2	6.01	100.11	0.0124	0.50
	3	5	8.01	100.06	0.0579	1.77
Famocid 40	2	2	4.01	100.18	0.0247	1.51
	4	2	5.99	99.90	0.0313	1.27
	3	5	7.95	99.47	0.0558	1.72
Famotin 40	2	2	3.96	99.20	0.0230	1.42
	4	2	5.98	99.82	0.0304	1.24
	3	5	8.02	100.34	0.0443	1.35
Facid 40	2	2	3.96	99.09	0.0199	1.23
	4	2	6.01	100.26	0.0156	0.63
	3	5	7.94	99.36	0.0544	1.67

a. Six independent analyses.

b. Standard analytical error.

Table 3 Determination of famotidine in pharmaceutical preparations by the fixed-time method using the standard addition technique

Formulation ^a	Amount added/ $\mu\text{g mL}^{-1}$	Amount taken/ $\mu\text{g mL}^{-1}$	Total amount found/ $\mu\text{g mL}^{-1}$	Recovery, %	SAE ^b	RSD, %
Topcid 40	1	1	1.98	99.38	0.0133	1.64
	2	4	6.01	100.12	0.0135	0.55
	3	5	7.96	99.52	0.0195	0.60
Famocid 40	1	1	1.97	98.85	0.0112	1.39
	2	4	5.99	99.95	0.0139	0.56
	3	5	7.97	99.62	0.0141	0.43
Famotin 40	1	1	1.96	98.05	0.0139	1.74
	2	4	6.01	100.17	0.0192	0.78
	3	5	7.96	99.52	0.0231	0.71
Facid 40	1	1	1.96	98.45	0.0147	1.82
	2	4	5.99	99.91	0.0152	0.62
	3	5	7.96	99.56	0.0174	0.53

a. Six independent analyses.

b. Standard analytical error.

Table 4 Determination of famotidine in commercial tablets by the initial-rate method and a reference method

Formulation	Proposed method		Reference method		t_{cal}^b	F_{cal}^c
	Recovery, ^a %	RSD, %	Recovery, ^a %	RSD, %		
Topcid 40	100.32	0.96	100.07	0.50	0.517	3.610
Famocid 40	99.61	0.73	99.78	0.45	0.485	2.576
Famotin 40	100.69	1.41	100.03	0.55	1.251	4.335
Facid 40	99.48	0.78	99.85	0.35	1.064	4.857

a. Average of six independent analyses.

b. t-value at 95% confidence level is 1.812.

c. F-value at 95% confidence level is 5.05.

Table 5 Determination of famotidine in commercial tablets by the fixed-time method and a reference method

Formulation	Proposed method		Reference method		t_{cal}^b	F_{cal}^c
	Recovery, ^a %	RSD, %	Recovery, ^a %	RSD, %		
Topcid 40	99.97	1.02	99.71	0.71	0.528	2.078
Famocid 40	100.19	1.19	100.00	0.54	0.357	4.724
Famotin 40	100.08	0.91	99.42	0.45	1.592	4.184
Facid 40	100.45	0.97	100.14	0.65	1.651	2.231

a. Average of six independent analyses.

b. t-value at 95% confidence level is 1.812

c. F-value at 95% confidence level is 5.05

intercept of the calibration line (at a fixed time of 12 min). This was established by drawing a joint confidence region (Fig. 5) at the 95% confidence level following the method of Mandel and Linnig.²² It is evident from the figure that the point for which the intercept is zero fell well within the ellipse, thus confirming no significant difference from zero.

The validity of the proposed methods was tested by adding a fixed amount of pure drug to preanalyzed dosage forms. The results obtained from the investigations are summarized in Tables 2 and 3, respectively, which indicated that the common additives and excipients did not interfere with the determination.

The initial-rate method and fixed-time method were applied to the determination of famotidine in commercial dosage forms. The concentration of the drug was computed from the corresponding regression equations. The results (Tables 4 and 5) obtained by the proposed method, were compared statistically with that of a reference method,⁷ revealing the fact that there is no significant difference in the performance of the methods regarding accuracy and precision.

Acknowledgements

The authors are grateful to Prof. Shafiullah, Chairman, Department of Chemistry, Aligarh Muslim University, Aligarh, for providing necessary research facilities. Thanks are also extended to M/s Wockhardt Ltd., India, for providing a gift sample of pure famotidine and to Dr. SM Jaweed Mukarram for his valuable cooperation to carry out this work.

References

1. Goodman and Gilman's, in "The Pharmacological Basis of Therapeutics", 9th ed., **1996**, McGraw Hill, New York, 904.
 2. U.S. Pharmacopoeia 23, National Formulary 18, United State, Pharmacopoeial Convention, Rockville, MD, **1995**, 65 and 1360.
 3. S. A. K. Ahmad, A. M. Kaway, and M. Nebsen, *Anal. Lett.*, **1999**, 32, 1403.
 4. B. V. Kamath, K. Shivram, and S. Vangani, *Anal. Lett.*, **1992**, 25, 2239.
 5. H. A. Mohammad, *Bull. Pharm. Sci. Assuit. Univ.*, **2000**, 23, 157.
 6. Z. A. Z. Ali, S. M. Raqi, and B. M. Ghassan, *J. Pharm. Biomed. Anal.*, **1999**, 21, 459.
 7. Y. K. Agarwal, K. Shivramchandra, G. N. Singh, and B. E. Rao, *J. Pharm. Biomed. Anal.*, **1992**, 10, 521.
 8. S. Raghuvver, C. M. R. Shrivastava, and D. K. Vatsa, *Indian Drugs*, **1992**, 29, 320.
 9. S. Zhang, W. Li, and C. Zhang, *Yaowu Fenxi Zazhi*, **1993**, 13, 150.
 10. X. X. Shen, W. Y. Xu, and J. Xu, *Zhongguo Yiyao Gongye Zazhi*, **1994**, 25, 76.
 11. S. Hussain, S. Khalid, V. Nagaraju, and N. R. Rao, *J. Chromatogr.*, **1996**, 743, 328.
 12. B. Carker, A. U. Tosun, and M. F. Sahin, *Pharm. Sci.*, **1997**, 3, 493.
 13. S. Gao, G. Liu, and S. Wang, *Yaowu Fenxi Zazhi*, **1991**, 11, 329.
 14. Z. Lu and J. Chen, *Yaowu Fenxi Zazhi*, **1997**, 17, 107.
 15. G. Carlucci, P. Mazzeo, and C. Vetusch, *Int. J. Pharm.*, **1994**, 102, 271.
 16. J. Novakovic, *J. Chromatogr.*, **1999**, 846, 193.
 17. A. J. Squella, C. Rivera, I. Lemus, N. Vergara, and J. Luis, *Microchim. Acta*, **1990**, 1, 343.
 18. J. Petkovic, D. Minic, Z. Koricanac, and J. Jovanovic, *Pharmazie*, **1998**, 53, 163.
 19. J. Roso, in "Advanced Physicochemical Experiments", **1964**, Sir Issac Pitman and Sons, London, 67.
 20. J. N. Miller, *Analyst*, **1991**, 116, 3.
 21. B. Morelli, *Analyst*, **1983**, 108, 870.
 22. J. Mandel and F. J. Linnig, *Anal. Chem.*, **1957**, 29, 743.
-