Application of Oxidizing Properties of Permanganate to the Determination of Famotidine in Pharmaceutical Formulations

Kanakapura Basavaiah* and Okram Zenita Devi

Department of Chemistry, University of Mysore, Manasagangothri, Mysore-570 006, India. basavaiahk@yahoo.co.in

Abstract. One titrimetric and two spectrophotometric methods are described for the determination of famotidine (FMT) in either pure form or in its pharmaceutical formulations. The methods are based on redox reaction between FMT and $KMnO_4$ in acid and alkaline media. In titrimetry, an acidified solution of FMT is titrated directly with permanganate. Direct spectrophotometry (method A) involves treating the alkaline solution of the drug with permanganate and measuring the bluish green product at 610 nm. In indirect spectrophotometry (method B), the drug solution is treated with a fixed concentration of permanganate in H_2SO_4 medium, and after a specified time, the unreacted permanganate is measured at 545 nm. The molar combining ratio in titrimetry and the optimum assay conditions are studied. Titrimetry is applicable over 1-10 mg range and the calculations are based on a 1:3 (FMT: $KMnO_4$) molar-ratio. In spectrophotometry, Beer's law is obeyed over 0.75-7.5 and 2.5-20 $\mu g\ mL^{-1}$ for method A and method B, respectively. The molar absorptivity values are calculated to be 2.79×10^4 and 1.62×10^4 L $mol^{-1}\ cm^{-1}$ for method A and method B, respectively, and the corresponding Sandell sensitivity values are 0.012 and 0.021 $\mu g\ cm^{-2}$. The limits of detection (LOD) and quantification (LOQ) are also reported for the spectrophotometric methods. The applicability of the developed methods was demonstrated by the determination of FMT in pure drug as well as in commercial dosage forms.
Keywords: Famotidine, assay, titrimetry, spectrophotometry, permanganate, pharmaceuticals.

Resumen. Se describen tres métodos, uno de titulación y dos espectrofotométricos, para la determinación de famotidina (FMT) en su forma pura o en sus formulaciones farmacéuticas. Los métodos están basados en la reacción redox entre FMT y $KMnO_4$ en medios ácido y básico. En el método de titulación, una solución acidificada de FMT se titula directamente con permanganato de potasio. De los métodos espectrofotométricos, el método directo A consiste del tratamiento de la solución alcalina de la droga con $KMnO_4$ y medición del producto verde azulado a 610 nm. En el método indirecto B, la solución de la droga se trata con una solución fija de $KMnO_4$ en ácido sulfúrico y, después de un tiempo específico, el $KMnO_4$ que no reaccionó se mide a 545 nm. Se estudió la proporción molar en el método de titulación, a fin de establecer las condiciones óptimas. Así, este método es aplicable en el intervalo de 1-10 mg, y los cálculos se basan en una proporción molar de FMT/$KMnO_4$ (1:3). En los métodos espectrofotométricos A y B, la Ley de Beer se cumple en los intervalos de 0.75-7.5 y 2.5-20 $\mu g\ mL^{-1}$, respectivamente. Los valores de absortividad molar se determinaron como 2.79×10^4 y 1.62×10^4 L $mol^{-1}\ cm^{-1}$ para los métodos A y B, respectivamente, y los valores correspondientes de sensibilidad fueron 0.012 and 0.021 $\mu g\ cm^{-2}$. Se describen igualmente los límites de detección (LOD) y cuantificación (LOQ) para los métodos espectrofotométricos. La aplicación de los métodos desarrollados se demostró en la determinación de FMT en su forma pura, así como en su forma de dosis comerciales.
Palabras clave: Famotidina, titulación, espectrofotometría, permanganato, fármacos.

Introduction

Famotidine (FMT), 3-[2-(diaminomethyleneamino) thiazol-4-ylmethylthio]-*N*-sulfamoylpropionamidine (Fig. 1), is a histamine H_2-receptor antagonist (H_2-RA) which competitively inhibits the action of histamine on the H_2-receptors of parietal cells and thereby reduces the gastric acid secretion under daytime and nocturnal basal conditions as well as secretion stimulated by food and pentagastrin. It is used for the short term treatment of duodenal ulcer and treatment of pathologic hypersecretory conditions like Zollinger-Ellison syndrome [1]. Therapeutic trials have shown that famotidine is approximately nine times more potent than cimetidine in inhibiting gastric acid secretion [2].

The drug is official in United State Pharmacopoeia [3] and British Pharmacopoeia [4] which describe potentiometric titrimetry and HPLC, respectively, for assay of famotidine in pharmaceutical formulations. A number of techniques have been reported for the determination of FMT in bulk, pharmaceutical dosage forms and in biological fluids and include UV-spectrophotometry [5], spectrofluorimetry [6], HPLC [7, 8], HPTLC [9, 10], capillary electrophoresis [11], differential

Fig. 1. Structure of famotidine.

pulse voltammetry [12] and potentiometry [13, 14]. Some of these methods [6-11, 13] are no doubt sensitive and selective, but require expensive instruments and accessories and solvents besides involving several cleanup procedures [8-11].

Titrimetry and visible spectrophotometry are still considered to be very convenient and economical techniques for routine analysis of the drug in pharmaceutical formulations. The famotidine content has earlier been determined titrimetrically based on the reaction of drug with iodate [15] and chloramine-T [16] as oxidimetric reagents. Visible spectrophotometric methods based on diverse chemical reactions have been proposed for the assay of FMT in pharmaceuticals. FMT is a good electron donor and procedures based on charge-transfer com-
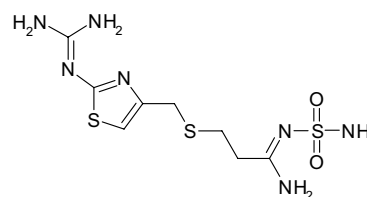
plex formation reactions with π acceptors such as chloranil, dichlorodicyanobenzoquinone and dichloronitrophenol [17], tetracyanoquinodimethane [18] and *p*-chloranilic acid [19, 20] have been reported. Extractive spectrophotometric procedures [21] based on ion pair complexation reaction with bromocresol green and bromothymol blue have also been proposed. Other visible spectophotometric methods based on reactions such as complex formation with copper (II) chloride [22], cupric acetate [23], palladium (II) chloride [24], condensation reaction with ninhydrin [25], formation of orange colored product with sodium nitroprusside [26], redox reaction with NBS - p-aminophenol [27], reduction of Folin-Ciocalteau reagent [28] and bromination involving brominating mixture [29] are found in the literature. Most of the above visible spectrophotometric methods suffer from one or other disadvantage such as use of organic solvents [18-22, 25], poor sensitivity [17, 19-20, 22-23, 26, 28-29], poor selectivity [28], use of expensive reagents [18], use of heating step [25], narrow linear range [25, 27], close pH control [21, 24], as indicated in Table 1. The present investigation aims to develop simple, sensitive and cost-effective methods for the determination of FMT in pure form and in dosage forms using titrimetric and spectrophotometric techniques with $KMnO_4$ as a reagent; which earlier has been used for the assay of FMT by kinetic spectrophotometry [30]. Reaction rate methods, in general, require scrupulous control of experimental variables and often known to give inaccurate and imprecise results. The present work reports the application of $KMnO_4$ for the assay of FMT by non-kinetic titrimetric and spectrophotometric methods. Several pharmaceutical compounds have been determined through this approach using $KMnO_4$ [31-41]. The proposed methods were demonstrated to be simple, selective and cost-effective compared to many reported methods including the official ones [3, 4].

Results and discussion

A close examination of the literature survey presented in introduction part reveals that except one kinetic spectrophotometric method, $KMnO_4$ has not been used for the spectrophotometric determination of FMT. $KMnO_4$ is a strong oxidizing agent and the Mn-containing products from redox reactions depend on the pH. Acidic solutions of permanganate are reduced to the faintly pink $[Mn(H_2O)_6]^{+2}$ and in an alkaline solution $KMnO_4$ is spontaneously reduced to bluish-green colored K_2MnO_4, where the manganese is in the (+6) oxidation state. Such oxidizing properties of $KMnO_4$ in different pH conditions are applied in the present work based on which one titrimetric and two spectrophotometric methods were developed for the determination of FMT. In titrimetry, FMT is directly titrated against $KMnO_4$ in sulphuric acid medium. And the end point was first appearance of pink color which remained for at least 2 minutes. The reaction stoichiometry was found to be 1:3 (FMT: $KMnO_4$). The spectrophotometric methods are based on the oxidation of FMT by $KMnO_4$ in either alkaline medium (method A) or acid medium (method B). Potassium perman-

ganate quantitatively oxidizes FMT in the NaOH medium and gets reduced to manganate ion – the bluish green colored chromogen [43, 44] which exhibited strong absorption maximum at 610 nm (Fig. 2). The increase in absorbance was measured at 610 nm (method A). In method B, the residual oxidant was measured at 545 nm after the reaction with FMT was ensured to be complete. In all the methods, the amount of $KMnO_4$ reacted corresponds to the amount of drug which served as the basis of quantification.

Optimization of variables

The experimental variables which provided accurate and precise results were optimized. The influence of each variable involved in the assays was examined.

Titrimetry

In titrimetry, the reaction was found to be stoichiometric in H_2SO_4 medium. Reproducible and regular stoichiometry was obtained when 1.0-2.3 M H_2SO_4 concentration was maintained. Hence, 5 mL of 5M H_2SO_4 solution in a total volume of 15 mL was found to be the most suitable concentration for a quantitative reaction between FMT and $KMnO_4$. The reaction stoichiometry was calculated to be 1: 3 (FMT: $KMnO_4$) in the 1-10 mg range. Below and above these limits irregular stoichiometries were obtained. Since the reaction between FMT and $KMnO_4$ was little bit slower, the titration was carried out by the dropwise addition of $KMnO_4$ solution and shaking vigorously during the titration, to the first appearance of pink color which persisted for 2 minutes.

Spectrophotometry
Method A
The experimental variables for the formation of stable and sensitive colored product were optimized. The sensitivity of the reaction was found to be influenced by the concentrations of $KMnO_4$ and NaOH. Optimum permanganate concentration was determined by varying the volume of 1000 μg mL^{-1} $KMnO_4$ from 0.5-3.0 mL in a total volume of 10 mL. It was found that as the concentration of $KMnO_4$ increased, the
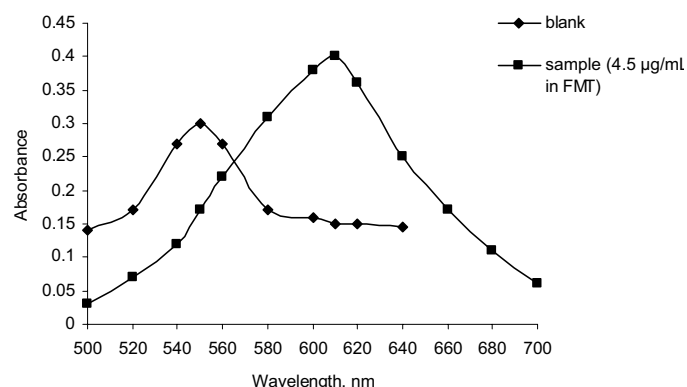

Fig. 2. Absorption spectra of method A (Bluish green color).

Table 1. Comparison of the performance characteristic of the existing spectrophotometric methods with those of the proposed methods for the determination of FMT in pharmaceuticals.

	Reagent/s used	Methodology	Linear range ($\mu g\ mL^{-1}$), and molar absorptivity ($L\ mol^{-1}\ cm^{-1}$)	Remarks	Ref.
1.	a) Chloranil, b) DDQ and c) DCNP	The increase in the absorbance is measured at 458, 460 and 425 nm, respectively.	50-500	Poor sensitivity and use of organic solvent	[17]
2.	Tetracyanoquino-dimethane	Green radical anion measured at 840 nm.	1.0-7.0	Uses expensive reagents and organic solvents	[18]
3.	a) P-chloranilic acid in methanol b) P-chloranilic acid in acetonitrile	C-T complex measured at 525 nm	a) 1.60-11.0 g% (w/v) b) 25-240	Less sensitive, uses acetonitrile which is very expensive	[19, 20]
4.	a) Bromocresol green b) Bromothymol blue	Ion-pair complex measured at 420 nm.	2.0-23 $\varepsilon = 5.0 \times 10^3$ 0.7-8.1 $\varepsilon = 1.2 \times 10^4$	Sensitive but requires close pH control and extraction, use of organic solvent	[21]
5.	Copper (II) chloride in methanolic medium	Blue color complex measured at 660 nm.	200-1200 $\varepsilon = 1.11 \times 10^2$	Less sensitive and use of organic solvent	[22]
6.	Cupric acetate	Complex measured at 630 nm.	50-1250	Poor sensitivity and use of organic solvent.	[23]
7.	Palladium (II)	Yellow color complex measured at 345 nm in the pH range 2.23-8.50.	17-200	Less sensitive and requires close pH control	[24]
8.	Ninhydrin in methanolic medium	Blue colored product measured at 590 nm.	5.0-30.0	Requires heating in a boiling water bath, narrow linear range and use of organic solvent.	[25]
9.	Sodium nitroprusside	Orange species fomed in alkaline medium measured at 498 nm.	50-500	Poor sensitivity	[26]
10.	NBS with p-aminophenol	The decrease in the absorption intensity of the colored product measured at 552 nm.	6.0-22.0	Two step reaction, longer reaction time and narrow linear range	[27]
11.	F-C reagent	Blue color product measured at 650 nm.	16-48	Narrow linear range and less sensitive	[28]
12.	Brominating mixture	Yellow color measured at 350	40-200	Less sensitive and measured at shorter wavelength	[29]
13.	$KMnO_4$ a) in alkaline medium	Bluish green color product measured at 610 nm	0.75-7.5 $\varepsilon = 2.79 \times 10^4$	Highly sensitive, no heating or extraction step, inexpensive instrumental setup, use of ecofriendly chemicals, and aqueous system	Present methods
	b) in acid medium	Unreacted permanganate color measured at 545 nm	2.5-20 $\varepsilon = 1.62 \times 10^4$		

NBS: N-bromosuccinimide; FC:Folin-Ciocalteu; DDQ:dichloro dicyano benzoquinone; DCNP: dichloronitrophenol.

sensitivity of the method also increased and at the same time the respective blank absorbance also increased concomitantly (Fig. 3). In the figure, it is shown that ΔA i.e. the difference in absorbance between sample and blank is more when 1 mL of 1000 $\mu g\ mL^{-1}$ $KMnO_4$ was used. Hence, 1 mL of 1000 μg

mL^{-1} $KMnO_4$ in a total volume of 10 mL was fixed as optimum taking into consideration the sensitivity of the reaction and minimum blank absorbance. NaOH concentration was found to be critical as sensitivity of the reaction was found to decrease with higher NaOH concentrations. However, when an
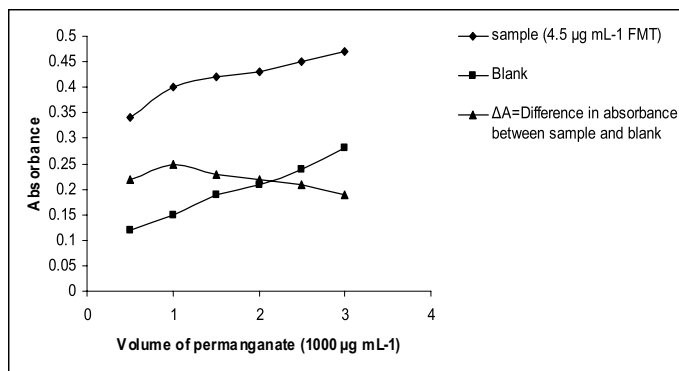
Fig. 3. Effect of $KMnO_4$ in method A.

overall NaOH concentration of 0.2-0.5 M was maintained at a drug concentration of 4.5 μg mL^{-1}, absorbance readings were maximum and found to be almost constant (Fig. 4) and further increase NaOH concentration gave poor sensitivity. Hence, 1 mL of 3M NaOH in a total volume of 10 mL was determined to be optimum for the reaction. The reaction was complete in 5 min and any delay up to 40 min had no effect on the absorbance (Fig. 5).

Method B
Preliminary experiments were performed to determine the concentration of $KMnO_4$ which gave maximum absorbance at 545
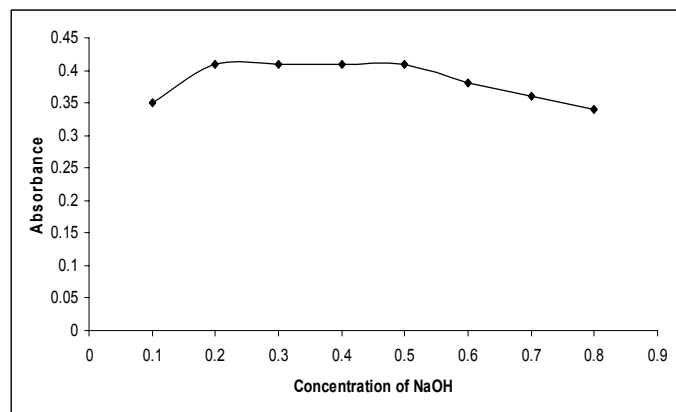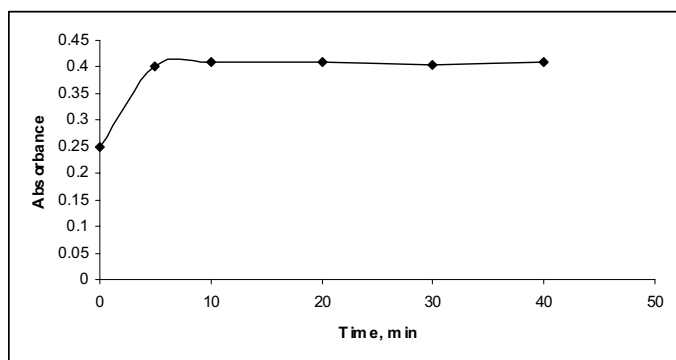

Fig. 4. Effect of NaOH in method A (4.5 μg mL^{-1} in FMT).

Fig. 5. Effect of time in method A (4.5 μg mL^{-1} in FMT).

nm in the acid medium employed and this was found to be 60 μg mL^{-1} (Fig. 6). Sulphuric acid is the most suitable acid, since it has no action on permanganate on dilution; and with hydrochloric acid, there is the likelihood of the formation of chlorine where some permanganate may be consumed [45]. Hence, the reaction between FMT and $KMnO_4$ was carried out in H_2SO_4 medium. When a fixed concentration of permanganate was reacted with increasing concentrations of FMT in H_2SO_4 medium, there occurred a concomitant fall in the concentration of permanganate as shown by the decreasing absorbance at 545 nm (Fig. 7). Hence, different concentrations of FMT were reacted with 1 mL of 600 μg mL^{-1} to determine the concentration range over which FMT could be determined. To investigate the effect of H_2SO_4 concentration on the reaction , 0.5-4.0 mL of 5 M H_2SO_4 were added to a fixed concentration of FMT (10 μg mL^{-1}) and $KMnO_4$ (60 μg mL^{-1}), and it was observed that constant absorbance readings were obtained when 1.0-3.0 mL of 5 M H_2SO_4 in a total volume of 10 mL were used (Fig. 8). Hence, 2 mL of 5 M H_2SO_4 was fixed. The reaction was found to be complete and quantitative when the reaction mixture was allowed to stand for 15 min, and beyond this standing time and up to 30 minutes, the absorbance remained constant (Fig. 9).
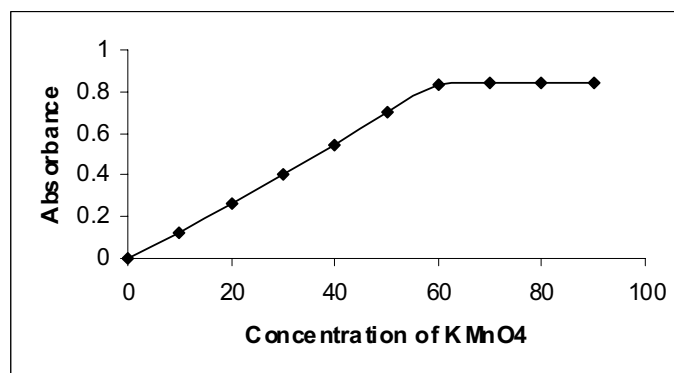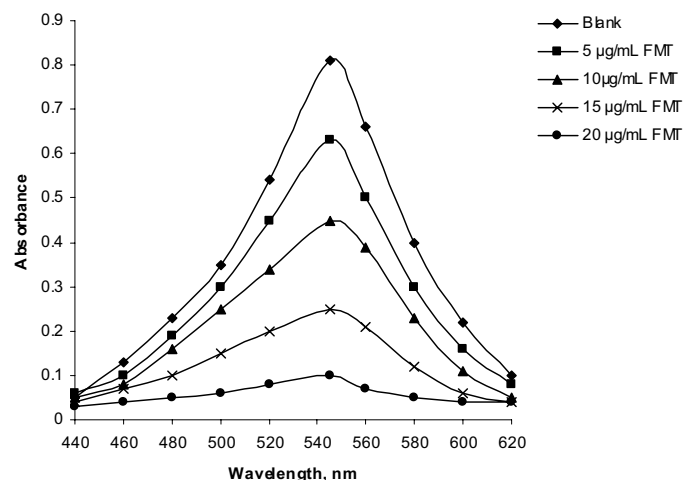

Fig. 6. Effect of $KMnO_4$ (method B).

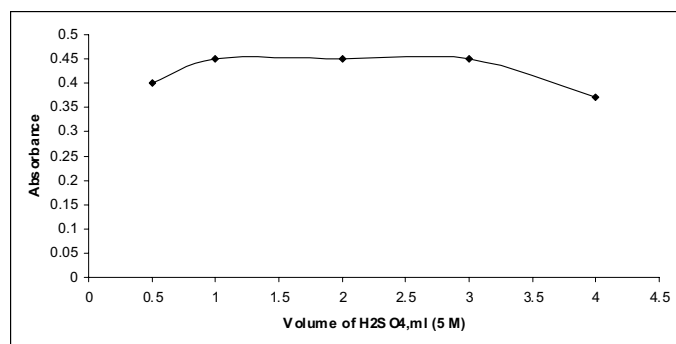**Fig. 7.** Effect of FMT concentration on the absorbance of 60 μg mL^{-1} $KMnO_4$ (Method B).

186 *J. Mex. Chem. Soc.* **2010**, *54(4)*

Kanakapura Basavaiah and Okram Zenita Devi

Fig. 8. Effect of H$_2$SO$_4$ in method B (10 µg mL^{-1} in FMT).
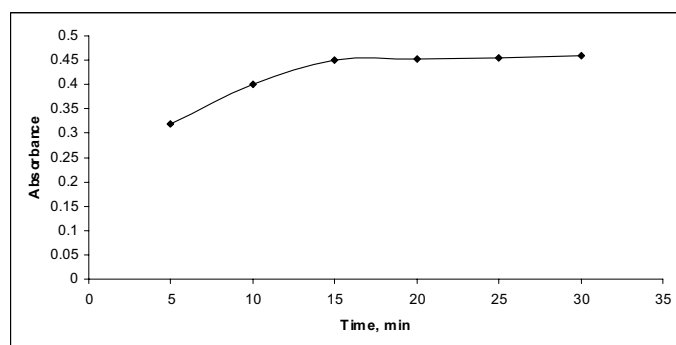

Fig. 9. Effect of time in method B (10 µg mL^{-1} in FMT).

Method validation

Analytical parameters of spectrophotometric methods

A linear relation was found to exist between absorbance and the concentration of FMT in the ranges of (0.75-7.5) µg mL^{-1} in method A (Fig. 10a) and (2.5-20) µg mL^{-1} in method B (Fig. 10b). The calibration graphs are described by the equation:

$$Y = a + b X$$

(Where Y = absorbance, a = intercept, b = slope and X = concentration in µg mL^{-1}) obtained by the method of least squares. Correlation coefficient, intercept and slope for the calibration data are summarized in Table 2. Sensitivity parameters such as apparent molar absorptivity and Sandell sensitivity values, the limits of detection and quantification calculated as per the current ICH guidelines [46] are compiled in Table 2 and are
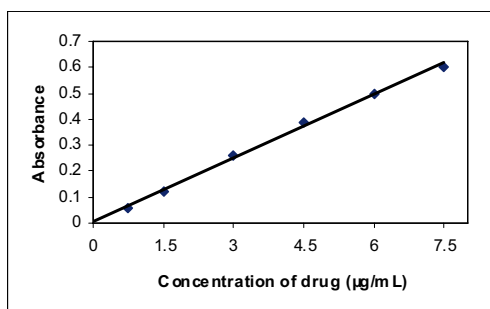
Table 2. Sensitivity and Regression Parameters.

Parameter	Method A	Method B
λ_{max}, nm	610	545
Linear range, µg mL^{-1}	0.75-7.5	2.5-20
Molar absorptivity (ε), L mol^{-1} cm^{-1}	2.79×10^4	1.62×10^4
Sandell sensitivity[a], µg cm^{-2}	0.012	0.021
Limit of detection (LOD), µg mL^{-1}	0.06	0.22
Limit of quantification (LOQ), µg mL^{-1}	0.17	0.65
Regression equation, Y[b]		
Intercept (a)	0.007	0.81
Slope (b)	0.08	0.04
Standard deviation of a (S$_a$)	0.03	0.126
Standard deviation of b (S$_b$)	0.004	0.008
Regression coefficient (r)	0.998	0.999

[a]Limit of determination as the weight in µg per mL of solution, which corresponds to an absorbance of A = 0.001 measured in a cuvette of cross-sectional area 1 cm^2 and l = 1 cm. [b]$Y = a + b X$, where Y is the absorbance, X is concentration in µg mL^{-1}, a is intercept, b is slope.

indicative of the excellent sensitivity of both methods. The limits of detection (LOD) and quantification (LOQ) were calculated according to the same guidelines using the formulae:

$$LOD = 3.3\sigma/s \text{ and } LOQ = 10\sigma/s$$

where σ is the standard deviation of five reagent blank determinations and s is the slope of the calibration curve.

Accuracy and precision

The accuracy and precision of the methods were evaluated by performing seven replicate analyses on pure drug solution at three different amount/concentration levels (within the working ranges). The relative error (%), an indicator of accuracy was within 3.0 and within day precision, also called the repeatability, expressed as relative standard deviation (RSD %) was less than 2.0 indicating high accuracy and repeatability of the methods. The results of the study are given in Table 3. The reproducibility of the methods also known as the day-to-day precision was evaluated by performing replicate analyses on pure drug solution at three levels over a period of five days,
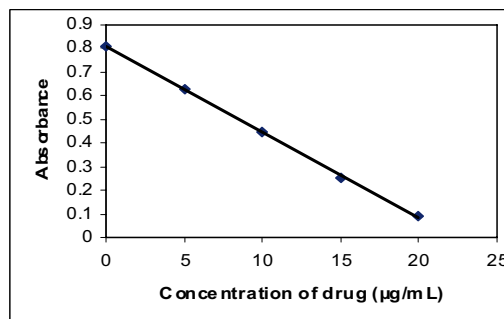

Fig. 10a. Calibration curve (method A).

Fig. 10b. Calibration curve (method B).

Table 3. Evaluation of intra-day and inter-day accuracy and precision.

Method[a]	FMT taken	Intra-day accuracy and precision			Inter-day accuracy and precision		
		FMT found	%RE	%RSD	FMT found	%RE	%RSD
Titrimetry	2.0	2.03	1.50	1.13	2.05	2.50	1.27
	4.0	4.04	1.00	1.01	4.08	2.00	1.08
	6.0	6.08	1.33	1.05	6.13	2.16	1.17
Spectrophotmetry Method A	1.5	1.53	2.01	1.14	1.55	3.33	1.19
	4.5	4.62	2.67	1.01	4.66	3.56	1.34
	7.5	7.35	2.00	0.89	7.75	3.33	1.23
Method B	5.0	4.95	1.00	1.13	4.87	2.60	1.35
	10.0	9.75	2.50	1.05	9.7	3.00	1.26
	15	14.7	2.00	0.97	14.42	3.86	1.16

RE: Relative error and RSD: Relative standard deviation.
[a]In titrimetry, FMT taken/found are in mg and they are $\mu g\ mL^{-1}$ in spectrophotometry.

preparing all solutions afresh. The day-to-day RSD values were less than 2% reflecting the usefulness of the methods in routine analysis.

Robustness and ruggedness
Method robustness was tested by making small incremental change in H_2SO_4 concentration in titrimetry and in spectrophotometry, H_2SO_4 and NaOH concentrations and reaction time were altered. To check the ruggedness, analysis was performed by four different analysts; and on three different spectrophotometers by the same analyst. The robustness and the ruggedness were checked at three different drug levels. The intermediate precision, expressed as percent RSD, which is a measure of robustness and ruggedness was within the acceptable limits as shown in the Table 4.

Effect of interferences
The effect of interferences was tested by placebo blank and synthetic mixture analyses. In titrimetry and spectrophotometric method B, there was no interference by the inactive ingredients. In method A, as most of the organic compounds react with permanganate in alkaline medium [47, 48], the results showed positive interference. However, the interference was successfully overcome by extraction with acetone as described under "experimental".

The analysis of synthetic mixture solution yielded percent recoveries which ranged between 94.01 and 96.74 with standard deviation of 1.18-1.43 in all the cases. The results of this study are presented in Table 5 indicating that the inactive ingredients did not interfere in the assay. These results further demonstrate the accuracy as well as the precision of the proposed methods.

Table 4. Robustness and ruggedness expressed as intermediate precision (%RSD).

Method	FMT taken, $\mu g\ mL^{-1}$	Method robustness			Method ruggedness	
		Parameter altered				
		H_2SO_4 (5M) mL[a] RSD, % (n = 3)	NaOH (3M) mL[b] RSD, % (n = 3)	Reaction time[c] RSD % (n = 3)	Inter-analysists' RSD, % (n = 4)	Inter-instruments' RSD, % (n = 3)
Titrimetry	3.0	1.31	—	—	1.09	1.24
	6.0	1.29	—	—	1.13	1.30
	9.0	1.34	—	—	0.98	1.17
Spectrophotometry Method A	1.5	—	1.22	1.19	0.87	1.49
	4.5	—	1.18	1.23	0.95	1.52
	7.5	—	1.24	1.15	1.04	1.41
Method B	10.0	1.29	—	1.26	0.94	1.23
	15.0	1.39	—	1.31	0.73	1.17
	20.0	1.27	—	1.24	0.89	1.28

[a]H_2SO_4 volumes used were 4.8, 5.0 and 5.2 mL in titrimetry and 1.8, 2.0 and 2.2 mL in spectrophotometric method B. [b]NaOH volumes used in spectrophotometric method A were 0.8, 1.0 and 1.2 mL. [c]Reaction time of 3, 5 and 7 min in spectrophotometric method A and 13, 15 and 17 min in spectrophotometric method B were employed

Table 5. Recovery of the drug from synthetic mixture.

Method	FMT in synthetic mixture taken[a]	FMT recoverd[b] (Percent ± SD)
Titrimetry	3.0	95.41 ± 1.21
	6.0	96.17 ± 1.25
	9.0	96.74 ± 1.18
Spectrophotometry Method A	1.5	94.01 ± 1.17
	4.5	95.83 ± 1.32
	7.5	94.78 ± 1.43
Method B	10.0	95.70 ± 1.34
	15.0	96.68 ± 1.21
	20.0	95.82 ± 1.18

[a]mg in titrimetry and µg mL^{-1} in spectrophotometry.
[b]Mean value of five determinations.

Application
Commercial tablets were successfully analyzed by the proposed methods. Co-formulated substances did not interfere in titrimetry and spectrophotometric method B. As huge interference was encountered in method A, FMT should be separated from the sample matrix by extraction with acetone and the drug reconstituted in NaOH before applying the procedure for assay as described under "experimental". This extraction step was found necessary to overcome the interference by the inactive organic ingredients in alkaline medium. For the purpose of comparison, the same batch pharmaceutical preparations were simultaneously analyzed by the reference method [2] which involved the titration of FMT in glacial acetic acid with 0.1N perchloric acid to potentiometric end point detection. The results are presented in Table 6. As shown in the table, the results of analysis obtained by the proposed methods are in accordance with those obtained by the reference method. The performance of the methods was further judged by applying Student's t-test for accuracy and F-test for precision. At the 95% confidence level, the calculated t- and F-values did not exceed the tabulated values (t = 2.77 and F = 6.39) suggesting that the proposed methods are as accurate and precise as the reference method.

Recovery studies
The accuracy and validity of the proposed methods were further ascertained by performing recovery studies. Preanalysed tablet powder was spiked with pure FMT at three levels (50, 100 and 150% of that found in tablet powder) and the total was determined by the proposed methods. The percent recovery of pure FMT added ranged between 96.59 and 98.67% with standard deviation of 1.17-1.33 (Table 7) indicating that the recovery was good, and that the co-formulated substance did not interfere in the determination.

Conclusions

The proposed methods are based on well established and characterized redox reactions. The titrimetric method is straightforward and fast when compared to the other methods reported earlier. Unlike most currently available spectrophotometric methods, the present methods are free from unwelcome steps such as heating or extraction and also from critical pH conditions. The spectrophotometric method B has high tolerance limit for common excipients found in tablet formulations and the interference encountered in method A could be easily overcome by extraction of FMT with acetone. An important advantage is the cost-effectiveness, since analysis can be performed with an inexpensive instrument along with eco-friendly chemicals in aqueous medium. Hence, the recommended procedures are well suited for the assay and evaluation of drug in pharmaceutical industrial quality control.

Experimental

Apparatus: All absorbance measurements were made on a Systronics model 106 digital spectrophotometer (Ahmedabad, India) provided with 1-cm matched quartz cells.
   Materials and reagents: All chemicals and reagents used were of analytical or pharmaceutical grade and distilled water was used throughout the experiment.

Table 6. Results of analysis of tablets by the proposed methods.

Tablet Brand name	Label claim, mg/tablet	Found[a] (Percent of label claim ± SD)			
		Reference method	Titrimetry	Spectrophotometry	
				Method A	Method B
Topcid-20[b]	20	97.52 ± 1.13	96.79 ± 1.17 t = 1.62 F = 1.26	95.68 ± 1.21 t = 2.48 F = 1.15	96.87 ± 1.15 t = 2.29 F = 1.04
Famocid-20 [c]	20	98.14 ± 1.02	96.56 ± 1.23 t = 2.22 F = 1.45	96.35 ± 1.19 t = 2.56 F = 1.36	95.87 ± 1.05 t = 2.39 F = 1.06

aMean value of five determinations.
[b]Torrent Pharmaceuticals Ltd., H. P, India; [c]Sun Pharmaceuticals Industries, Jammu, India.
The value of t (tabulated) at 95 % confidence level and for four degrees of freedom is 2.77.
The value of F (tabulated) at 95 % confidence level and for four degrees of freedom is 6.39.

Table 7. Accuracy assessment by recovery experiments.

Method	Tablet studied	FMT in tablet[a]	Pure FMT added[a]	Total found[a]	Pure FMT recovered[b] Percent ± SD
Titrimetry	Topcid-20	4.0	2.0	5.95	97.50 ± 1.29
		4.0	4.0	7.88	97.00 ± 1.23
		4.0	6.0	9.83	97.17 ± 1.18
Spectrophotometry Method A	Topcid-20	3.0	1.5	4.48	98. 67 ± 1.25
		3.0	3.0	5.90	96.70 ± 1.17
		3.0	4.5	7.37	97.11 ± 1.33
Method B	Topcid-20	5.0	2.5	7.43	97.20 ± 1.31
		5.0	5.0	9.83	96.59 ± 1.28
		5.0	7.5	12.27	96.93 ± 1.22

[a]mg in titrimetry and µg mL^{-1} in spectrophotometry.
[b]Mean value of three measurements.

Standard FMT solution
Pharmaceutical grade FMT certified to be 99.98 % pure was received as gift from Cipla India Ltd, Mumbai, India, and used as received. Standard FMT solutions (1 mg mL^{-1}, 15 µg mL^{-1} and 50 µg mL^{-1}) were prepared by dissolving calculated quantity of pure drug in 0.1 M H_2SO_4 for titrimetry and spectrophotometric method B and in 0.1 M NaOH for spectrophotometric method A.

Two brands of tablets containing FMT, Topcid-20 (Torrent Pharmaceuticals Ltd., H. P, India) and Famocid-20 (Sun Pharmaceuticals Industries, Jammu, India), used in the investigation were purchased from local commercial sources.

Potassium permanganate (0.01 M, 1000 µg mL^{-1} and 600 µg mL^{-1}).

An approximately 0.01 M solution was prepared by dissolving 790 mg of $KMnO_4$ (Merck, Mumbai, India) in water and diluting to 500 mL in a calibrated flask, and standardized using H.A Bright's procedure [42] and used in titrimetry. This solution was then diluted appropriately with water to get 1000 and 600 µg mL^{-1} working concentrations for spectrophotometric method A and method B, respectively.

Sulphuric acid (5 M and 0.1 M)

Concentrated acid (S.D. Fine Chem, Mumbai, India, sp. gr. 1.84) was appropriately diluted with water to get the required concentrations.

Sodium hydroxide (3 M and 0.1 M)

Prepared by dissolving calculated quantity of the chemical (Merck, Mumbai, India) in water.

Recommended procedures

Titrimetry
Different volumes (1-10 mL) of standard solution containing 1 mg mL^{-1} FMT were taken in a 100 mL titration flask and the volume was made up to 10 mL with 0.1 M H_2SO_4. Five mL of 5M H_2SO_4 were added and the content titrated against 0.01 M $KMnO_4$. The titration was performed by drop wise addition of $KMnO_4$ with continuous shaking, and the end point was the

first appearance of pink color which persisted for at least 2 minutes.

The amount of FMT in the aliquot was computed from the following formula:

$$\text{Amount (mg)} = VM_wS/n$$

where V = mL of $KMnO_4$ consumed
M_w = relative molecular mass of drug
S = strength of $KMnO_4$, moles/L
n = number of moles of $KMnO_4$ reacting with per mole of FMT.

Spectrophotometry
Method A: Different aliquots of 0.5, 1.0, 2.0, 3.0, 4.0 and 5.0 mL of standard FMT solution (15 µg mL^{-1}) were transferred into a series of 10 mL standard volumetric flasks and the total volume in each flask was adjusted to 5 mL with 0.1 M NaOH. To each flask, 1 mL of 3M NaOH followed by 1 mL of 1000 µg mL^{-1} $KMnO_4$ were added. The content of each flask was mixed well and kept aside for 5 minutes with occasional shaking. The volume was made up to the mark with distilled water and the absorbance was measured at 610 nm *Vs* reagent blank prepared in a similar manner.

Method B: Different aliquots (0.0, 0.5, 1.0, 2.0, 3.0 and 4.0 mL) of standard 50 µg mL^{-1} FMT solution were accurately measured and transferred into a series of 10 mL volumetric flasks by means of a microburette and the total volume was adjusted to 5 mL with 0.1 M H_2SO_4. To each flask 2 mL of 5 M H_2SO_4 and 1 mL of 600 µg mL^{-1} $KMnO_4$ were added, the latter using microburette. The content of each flask was mixed well and kept aside for 15 minutes. The volume was made up to the mark with distilled water and the absorbance was measured at 545 nm *vs* water.

Calibration graphs were prepared by plotting either the increasing absorbance values in method A or decreasing absorbance values in method B *versus* concentration of FMT.

The concentration of the unknown was read from the respective calibration graph or deduced from the regression equation derived using the absorbance-concentration data.

Procedure for the assay of famotidine in pharmaceutical preparations

Twenty tablets were weighed accurately and ground into a fine powder. An accurately weighed amount of the powdered tablet equivalent to 100 mg of FMT was transferred to a 100 mL calibrated flask and shaken with 60 mL of 0.1 M H_2SO_4 (titrimetry and spectrophotometric method B) for about 20 min, then made up to the mark with the same solvent and mixed; and filtered using a Whatman No. 42 filter paper. First 10 mL portion of the filtrate was discarded, and a convenient aliquot (say 5 mL) was taken and the assay completed according to the titrimetric procedure described above. The tablet extract containing 1 mg mL^{-1} FMT was then diluted stepwise with 0.1 M H_2SO_4 to obtain working concentration of 50 µg mL^{-1} in FMT for spectrophotometric method B and the analysis was completed using the procedure describe above (method B). In method A, an accurately weighed amount of the powdered tablet equivalent to 5 mg of FMT was extracted with three 10 mL portions of acetone by shaking for 10 min each time and filtered using a Whatman No. 42 filter paper. The filter paper was washed several times with small portions of acetone. The filtrate and washings were evaporated to dryness. The residue was dissolved in 0.1 M NaOH and diluted up to the mark of a 50 ml volumetric flask. The resulting solution was diluted with 0.1 M NaOH to obtain 15 µg mL^{-1} in FMT and the assay was completed by following the recommended procedure (method A).

Placebo blank analysis

A placebo blank of the composition: talc (10 mg), starch (5 mg), acacia (5 mg), methyl cellulose (10 mg), sodium citrate (5 mg), magnesium stearate (10 mg) and sodium alginate (5 mg) was made and its solution was prepared as described under 'Procedure for the assay of famotidine in pharmaceutical preparations', and then subjected to analysis using the procedures described above.

Procedure for the determination of famotidine in synthetic mixture

To the placebo blank of the composition described above, 100 mg of FMT was added and homogenized, transferred to a 100 mL standard flask and solution prepared as described under tablets. The solution was mixed well and filtered using a Whatman No. 42 filter paper. The resulting solution was assayed (n = 5) by titrimetry according to the procedure described above. The synthetic mixture solution (1 mg mL^{-1} in FMT) was then diluted stepwise with 0.1 M H_2SO_4 to obtain working concentration of 50 µg mL^{-1} in FMT for spectrophotometric method B. A convenient aliquot was then subjected

to analysis. In method A, 5 mg of FMT was added to the placebo blank of the composition described above and homogenized and followed the same extraction procedure which was described under 'Procedure for the assay of famotidine in pharmaceutical preparations' and then subjected to analysis using the procedure described above. These analyses were performed to study the effect of excipients such as talc, starch, acacia, methyl cellulose, sodium citrate, magnesium stearate and sodium alginate on the performance of the methods.

Acknowledgements

References

1. Goodman & Gilman's "*The Pharmacological Basis of Therapeutics*", 9th Ed., McGraw Hill, New York, **1996**, 904.
2. Campoli-Richard, D. M.; Clissold, S. P. *Drugs*. **1986**, *32*, 197-221.
3. United State Pharmacopoeia 23, National Formulary 18, United States, Pharmacopoeial Convention, Rockville, MD, **1995**, *65*, 1360.
4. British Pharmacopoeia, The Stationary Office London, **1998**, 572.
5. Sahu, R.; Preeti, N.; Bhattacharya, S.; Deepti, J. *Indian J. Pharm. Sci.* **2006**, *68*, 503-506.
6. Walash, M. I.; El-Brashy, A.; El-Enany, N.; Kamel, M. E. *J. Fluor.* **2008**, *19*, 333-344.
7. Zarghi, A.; Shafaati, A.; Foroutan, S. M.; Khoddam, A. *J. Pharm. Biomed. Anal.* **2005**, *39*, 677-680.
8. Mutaz, A.; Sheikh, S.; Hanan, A. N.; Adnan, B. A. *Anal. Lett.* **1989**, *22*, 2501-2510.
9. Campbell, A. N.; Sherma, J. *J. Liq. Chromatogr. Rel. Technol.* **2003**, *26*, 2719-2727.
10. Novakovic, J. *J. Chromatogr.* **1999**, *846*, 193-198.
11. Ibrahim, D. A.; Samiha, A. H.; Ashraf, M. M.; Ahmed, I. H. *Int. J. Biomed. Sci.* **2007**, *3*, 123-130.
12. Squella, J. A.; Rivera, C.; Lemus, I.; Nunez-Vergara, L. J. *Microchim. Acta* **1990**, *100*, 343-348.
13. Ayad, M.; Shalaby, A.; Hisham, E. J. M. *J. Pharm. Biomed. Anal.* **2002**, *29*, 247-254.
14. Magda, M. A.; Abdalla, S.; Hisham, E. A.; Heba, M. E. *J. Pharm. Biomed. Anal.* **2002**, *29*, 247-244.
15. Basavaiah, K.; Prameela, H. C. *Bulg. Chem. Ind.* **2003**, *74*, 50-55.
16. Basavaiah, K.; Prameela, H. C. *Bulg. Chem. commun.* **2003**, *35*, 37-42
17. Kamath, B. V.; Shivram, K.; Saroj, V. *Anal. Lett.* **1992**, *25*, 2239-2247.
18. Sheikha Al-Ghannam, F. B. *J. AOAC Int.* **2002**, *85*, 1003-1008.
19. Chukwurah, B. K.; Ajali, U. *Boll. Chim. Farm.* **2001**, *140*, 354-360.
20. Mohammad, H. A. *Bull. Pharm. Sci. (Assiut University)*, **2000**, *23*, 157-163
21. Abu Zuhri, A. Z.; *Shubietah,* R. M.; Badah, G. M. *J. Pharm. Biomed. Anal.* **1999**, *21*, 459-465.
22. Basavaiah, K.; Prameela, H. C. *Indian Pharmacist*, **2004**, *3*, 59-61.

23. Guvener, B.; Ates, S. *Acta Pharm. Turc* **1988**, *30*, 67-68.
24. Zagorka, K.; Tatijana, J.; Jelena, P.; Dragica, M. *J. Serb. Chem. Soc.* **2004,** *69*, 485-491.
25. Nafisur, R.; Mohammad, K. *Farmaco* **2003**, *58*, 1045-1050.
26. Agarwal, Y. K. K.; Shivaramchandra, K.; Rao, G. N. *J. Pharm. Biomed. Anal.* **1992**, *10*, 521-523.
27. Ibrahim, A.; Darwish, S. A.; Hussein, A. M.; Mahmoud, A. H. I. *Acta Pharm.* **2007**, *58*, 87-97.
28. Rao, G. R.; Kanjilal, G.; Mohan, K. R. *Analyst* **1978**, *103*, 521-523.
29. Rami, N. R.; Prabhavathi, K.; Bhaskar, R. Y. V.; Chakravarthy, I. E. *Indian J. Pharm. Sci.* **2006**, *68*, 645-647.
30. Rahman, N.; Kashif, M. *Anal. Sci.* **2003**, *19*, 907-911.
31. Tammilehto, S. A. *J. Pharm. Pharmacol.* **1980**, *32*, 524.
32. Murugesan, A.; Venkappaya, D. *Curr. Sci.* **1983**, *52*, 249.
33. Vinay, K. B.; Revanasiddappa, H. D.; Zenita, O.; Basavaiah, K. *CI&CEQ* **2009**, *15*, 149-157.
34. Zenita, O.; Basavaiah, K.; Vinay, K. B. *CI&CEQ* **2010**, *16*, 97-102.
35. Tharpa, K.; Basavaiah, K.; Vinay, K. B. *Jordan J. Chem.* **2009**, *4*, 387-397.
36. Basavaiah, K.; Rajendraprasad, N.; Tharpa, K.; Anilkumar, U. R.; Hiriyanna, S. G.; Vinay. K. B. *J. Mex. Chem. Soc.* **2009**, *53,* 34-40.
37. Basavaiah. K.; Tharpa, K.; Anil Kumar, U. R.; Rajendraprasad, N.; Hiriyanna, S.; Vinay, K. B. *Arch. Pharm. Res.* **2009**, *32*, 1271-1279.
38. Abdellatef, H. E. *J. Pharm. Biomed. Anal.* **2002**, *29*, 835-842.
39. Reddy, M. N.; Reddy, V. P. N.; Reddy, P. J. C.; Murthy, T. K.; Srinivasa, Y. *Antiseptic* **2002**, *99*, 88.
40. Al-Ghanman, S. M.; Belal, F. *Farmaco* **2001**, *56*, 677-681.
41. Sastry, C. S. P.; Vijaya, R. T.; Satyanarayana, A. *Indian J. Pharm. Sci.* **1998**, *60*, 55-58.
42. Bright, H. A. *Vogel's Text Book of Inorganic Analysis Including Elementary Instrumental Analysis*, 3rd Ed., **1961**, *280.*
43. Mann, F. G.; Sounders, B.C. *Int. New Impressions*, 4th Ed., Orient Longman, Cambridge, **1974**, *85*.
44. Sharma, B. K. *Instrumental Methods of Analysis*, 18th Edn., Goel Publishing Home, Meerut, **1994**, *114*.
45. Basset, J.; Denney, R. C.; Jeffery, G. H.; Mendham, J. *Vogel's Text Book of Inorganic Analysis Including Elementary Instrumental Analysis*, 4th Ed., **1978**, *348*.
46. International Conference On Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, *Validation of Analytical Procedures: Text and Methodology Q2(R 1)*, Complementary Guideline on Methodology dated 06 November 1996, incorporated in November, **2005**, London.
47. Kolthoff, I. M.; Belcher, R.; Stenger, V. A.; Matsuyuma, G. *Volumetric Analysis,* Interscience Publishers, Inc., New York, Vol. 3, **1957,** 113-118.
48. Nanji, D. R.; Norman, A. G. *J. Soc. Chem. Ind. (London)* **1926**, *45*, 337T.