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Potentiometric determination of famotidine in pharmaceutical formulations

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Abstract

Two new potentiometric methods for determination of famotidine in pure form and in its pharmaceutical tablet form are developed. In the first method, the construction of plasticised poly(vinyl chloride) (PVC) matrix-type famotidine ion-selective membrane electrode and its use in the potentiometric determination of famotidine in pharmaceutical preparations are described. It is based on the use of the ion-associate species, formed by famotidine cation and tetraphenyl borate (TPB) counterion. The electrode exhibited a linear response for 1×10^{-3}–1×10^{-5} M of famotidine solutions over the pH range 1–5 with an average recovery of 99.26% and mean standard deviation of 1.12%. Common organic and inorganic cations showed negligible interference. In the second method, the conditions for the oxidimetric titration of famotidine have been studied. The method depends on using lead(IV) acetate for oxidation of the thioether contained in famotidine. The titration takes place in presence of catalytic quantities of potassium bromide (KBr). Direct potentiometric determination of 1.75×10^{-2} M famotidine solution showed an average recovery of 100.51% with a mean standard deviation of 1.26%. The two methods have been applied successfully to commercial tablet. The results obtained reveal good percentage recoveries, which are in good agreement with those obtained by the official methods.

Keywords: Famotidine; Ion-selective electrode; Tetraphenyl borate; Lead(IV) acetate; Potentiometric titration; Pharmaceutical analysis

1. Introduction

The official drug famotidine, (*N^2(aminosulphonyl)*-3-[[[2-[(*diamino methylene*)*amino*]*thiazol*-7-*yl*]*methyl*]*thio*]*propanamidine*), is histamine-H_2 receptor antagonist, which inhibits gastric acid secretion and also inhibits the secretion induced by acetylcholine and gastrin.

Several procedures have been reported in the literature for the analysis of famotidine. These methods are spectrophotometry [1–5], fluorimetry [6], liquid chromatography [7–10], electrophororesis [11], polarography [12], voltammetry [13] and potentiometric procedure using palladium(II) chloride as titrant [14]. The U.S.P. XXIII [15] and BP [16] specify non-aqueous titration technique detecting the end point potentiometrically for determination of famotidine.

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Although ion-selective electrodes (ISEs) have found many successful applications in pharmaceutical analysis [17] mainly because of their low cost, ease of use and maintenance and the simplicity and speed of the assay procedures, it has not been applied yet to the determination of famotidine. It is usually possible to develop procedures for the determination of drugs in pharmaceutical preparations that need only a pre-dilution step with a suitable buffer (e.g. injection preparations) or dissolution of tablets in the measuring solvent. Turbidity due to the matrix is not usually a problem, so that even the filtration step can be avoided. Usually, the potentiometric methods can be simple and fast for pharmaceutical analysis when suitable sensor is available.

The propose of the present work is to describe the development of two accurate and selective potentiometric methods for determination of famotidine in pure drug and pharmaceutical tablets.

2. Experimental

2.1. Apparatus

- Jenway 3010 pH/mV meter with double junction platinum electrode.
- Jenway 3010 pH/mV meter, with famotidine–tetraphenyl borate (TPB)–poly(vinyl chloride) (PVC) membrane electrode in conjunction with double junction Ag/AgCl electrode (Orion 90-02), containing 10% w/v potassium nitrate in the outer compartment.
- An Orion 91 02 glass–calomel combination electrode was used for pH adjustment.

All potentiometric measurements were carried out at 25 ± 1 °C with constant magnetic stirring.

2.2. Materials and reagents

All reagents were of analytical grade bidistilled water was used.

1. Famotidine authentic (determined by the U.S.P. XXIII [15] method and was found to be 99.5%) and Servipep® tablets (labelled to contain 20 mg famotidine per tablet) were obtained from Swisspharma, Egypt S.A.E. Cairo.
2. PVC (Aldrich).
3. Sodium tetraphenyl borate (NaTPB) (Aldrich), 1×10^{-2} aqueous solution.
4. Bis(2-ethylhexyl sebacate) (Fluka).
5. Acetic acid (99.5%) (El-Nasr Chemical Co., Egypt), dilute (10% v/v) solution.
6. Lead(IV) acetate (Sigma), 0.1 (1.16% w/v) solution in glacial acetic acid.
7. Potassium bromide (KBr) (El-Nasr Chemical Co., Egypt), 2.5×10^{-3} M solution in bidistilled water was prepared and used in preparation of 2.5×10^{-4} M solution in 70% acetic acid.

2.3. Standard drug solutions

2.3.1. Solution for method 1 (procedure used ISE)

0.1 M (3.7% w/v) solution, was prepared in dilute acetic acid then different standard solutions (1×10^{-2}–1×10^{-6} M) were prepared by serial dilution of the stock solution. The solution is stable for at least 1 week if stored in a cool and dark place.

2.3.2. Solution for method 2 (procedure using lead tetra-acetate)

1.75×10^{-2} M solution, was prepared by dissolving 59 mg of famotidine in 10-ml bidistilled water. The solution was prepared fresh daily.

2.4. General procedures

2.4.1. Method 1 (procedure using ISE)

2.4.1.1. Sensor preparation. A 50-ml aliquot of 1×10^{-2} M famotidine solution in dilute acetic acid was mixed with 50 ml of 1×10^{-2} M aqueous NaTPB solution with continuous stirring through the addition process. The white ion-pair precipitate (Fig. 1) was filtered off through G_4 sintered glass crucible and washed thoroughly with deionised water, then dried at room temperature for 24 h. The dried ground ion-pair has a melting point of 74–76 °C.

2.4.1.2. Electrode preparation. The membrane was prepared by dissolving 190 mg of powdered PVC, 0.35 ml of the plasticiser [bis(2-ethylhexyl sebacate)] and 10 mg of the ion-pair in 5 ml THF. The solution was poured into a petri-dish (3 cm in diameter) and covered with a filter paper. The solvent was allowed to evaporate slowly at room temperature. Punched circular membrane was attached to polyethylene tube (8 mm in diameter) in an electrode configuration according to the procedure of Moody et al. [18].

A mixture of equal volumes of 1×10^{-3} M solution of famotidine and potassium chloride (KCl) was used as internal reference solution in which Ag/AgCl reference electrode was dipped. The constructed electrode was pre-conditioned after preparation by soaking for at least 24 h in 1×10^{-3} M drug solution and stored in the same solution.

2.4.1.3. Electrode calibration. Ten millilitre aliquots of 1×10^{-1}–1×10^{-6} M standard solution of famotidine were transferred into a 50 ml beaker and the membrane electrode in conjunction with Ag/AgCl reference electrode were immersed in the solution. The measured potential was plotted against the logarithm of drug concentration. The electrode was washed with deionised water blotted with tissue paper between measurements.

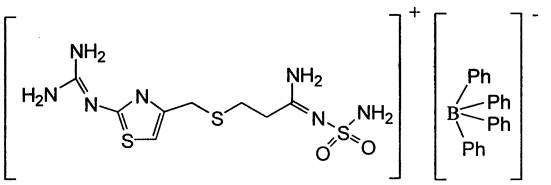


Fig. 1. Famotidine–TPB complex.

Table 1
Selectivity coefficient for some common cations with famotidine–TPB–PVC membrane electrode

Interferent	$K^{pot}_{famot,j}$
Ammonium chloride	1.3×10^{-2}
Sodium chloride	1.4×10^{-2}
Magnesium chloride	1.3×10^{-2}
Potassium chloride	1.8×10^{-2}
Calcium chloride	1.8×10^{-2}
Lysine	1×10^{-2}
Leucine	8.5×10^{-3}
Tryptophane	1×10^{-3}
Valine	6.9×10^{-3}
Oxalic acid	4.9×10^{-2}

2.4.1.4. Effect of pH. The effect of pH on the potential of the electrode system was studied using two pH/mV metres. The combined glass calomel electrode was connected to one instrument and the famotidine–TPB–PVC membrane with the double junction Ag/AgCl reference electrode was connected to the second instrument. Thirty millilitre aliquots of 1×10^{-3} and 1×10^{-4} M famotidine were transferred into a 100-ml beaker where the three electrodes were immersed, the potential reading corresponding to different pH values were recorded. The pH was gradually increased or decreased by the addition of small aliquots of dilute solutions of sodium hydroxide or hydrochloric acid, respectively and the mV–pH was plotted.

2.4.1.5. Interference effect. The response of the electrode was also examined in the presence of a number of organic ions. The potentiometric selectivity coefficients $K^{pot}_{famot,j}$ were used to evaluate the degree of interference [19,20]. A 9.0-ml aliquot of distilled water was placed in a 50-ml beaker where the famotidine–TPB–PVC membrane electrode and the double junction Ag/AgCl electrode were immersed. The potential response upon addition of 1.0 ml aliquot of 1×10^{-2} M solution of the interferent was recorded and compared with that of 1×10^{-3} M pure famotidine solution. The selectivity coefficients were calculated using Eisenman–Nicolsky equation:

$$-\log K^{pot}_{drug,j} = \frac{E_1 - E_2}{S},$$

where, E_1 and E_2 are the potential readings observed after 1 min due to the same concentration of famotidine and the interferent, respectively and S is the slope of the famotidine calibration graph (mV/concentration decade).

Results obtained are given in Table 1 and reasonable selectivity for famotidine was observed in presence of many interferents.

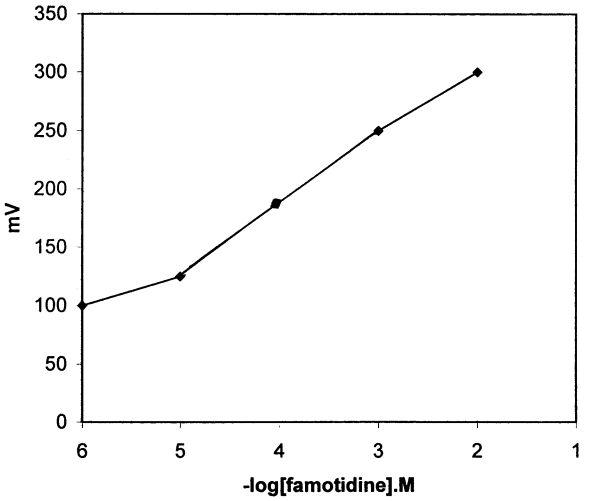


Fig. 2. Calibration graph for famotidine–TPB–PVC membrane electrode.

Table 2
Critical response characteristics of famotidine–TPB–PVC membrane electrode

Parameters	Famotidine–TPB–PVC membrane electrode
Slope (mV per decade)	59 ± 1
Intercept (mV)	407
Correlation coefficient (r)	0.997
Linear range (M)	1×10^{-3}–1×10^{-5}
Working pH range	1–5
Response time for 10^{-4} M drug (s)	15
Life time (day)	7

2.4.1.6. Determination of famotidine in pharmaceutical tablets. Twenty tablets were powdered and shaken with 50 ml glacial acetic acid and diluted with water to obtain different concentrations in the range of 1×10^{-3}–1×10^{-5} M and the prepared solutions were adjusted to pH 5. The membrane and reference electrodes were immersed in the prepared solutions. The electrode system was allowed to equilibrate with stirring and the potential was recorded and compared with the calibration graph.

2.4.2. Method 2 (procedure using lead tetra-acetate)

2.4.2.1. Construction of potentiometric curves. One millilitre of standard solution (for titrimetric procedure using lead tetra-acetate) was added to 70 ml of 70% solution of acetic acid water. KBr (2.5×10^{-6} M) was added and the solution was titrated with 0.1 N lead tetra-acetate solution. The titrant was added at a rate of 1 ml/min and the end point was detected potentiometrically. The reaction rate was compared to that of the usual neutralization reaction.

2.4.2.2. Procedure for pharmaceutical tablets. Ten tablets were finely powdered and an accurate weight equivalent to 8.43 mg famotidine was shaken well with 70 ml glacial acetic acid and the mixture was centrifugated to obtain clear solution, then diluted to 100 ml with bidistilled, the procedure was completed as mentioned in Section 2.4.2.1.

3. Results and discussion

3.1. Method 1 (procedure used ISE)

3.1.1. Nature and response characteristics of the electrode

Famotidine reacts with NaTPB to form an insoluble ion-associate. Elemental analysis indicated a molar ratio of (1:1) drug to counterion and that agreed well with results obtained.

The electrochemical performance characteristics of the constructed electrode were evaluated according to IUPC recommendation [19] using the following electrochemical cells:

Ag–AgCl/KCl (1×10^{-3} M)
+ famotidine (1×10^{-3} M)‖famotidine
–TPB–PVC membrane‖test solution/Ag
–AgCl reference electrode.

The calibration graph, Fig. 2, exhibits a Nernstian response for 1×10^{-3}–1×10^{-5} M famotidine solutions with cationic slope of 59 ± 1 mV per decade change in concentration, (Table 2).

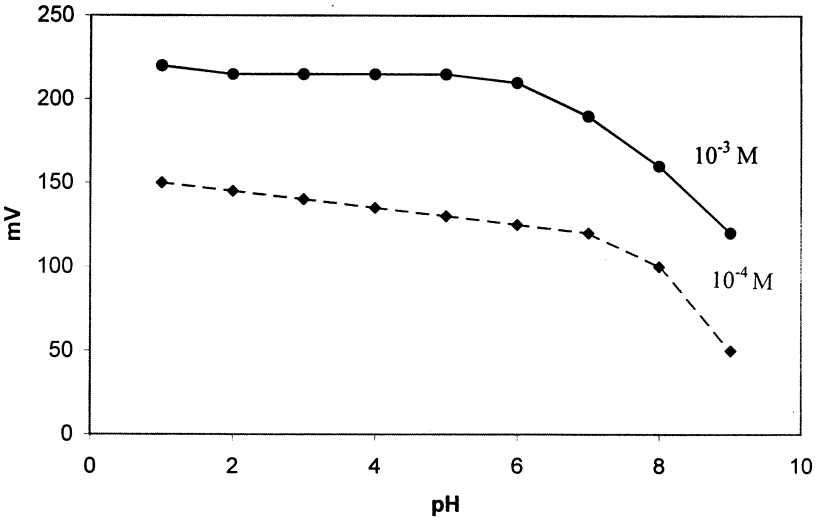


Fig. 3. Effect of pH on the potential response of famotidine–TPB–PVC membrane electrode.

The dynamic response time of the electrode systems was tested for 1×10^{-2}–1×10^{-4} M famotidine solutions. Sequence of the measurement was from low to higher concentration. The required time for the electrode to reach value within ± 1 mV from the final equilibrium potential after increasing the level of the drug concentration to 10-fold was fairly short and 90% of the final steady potential was reached after up to 15 s.

The potential displayed by famotidine–TPB–PVC membrane electrode for consecutive measurements of 1×10^{-3}–1×10^{-5} M-famotidine did not vary by more than ± 0.5 mV ($n = 10$) in the same day. The calibration slope did not vary by more than ± 1 mV per decade change of concentration.

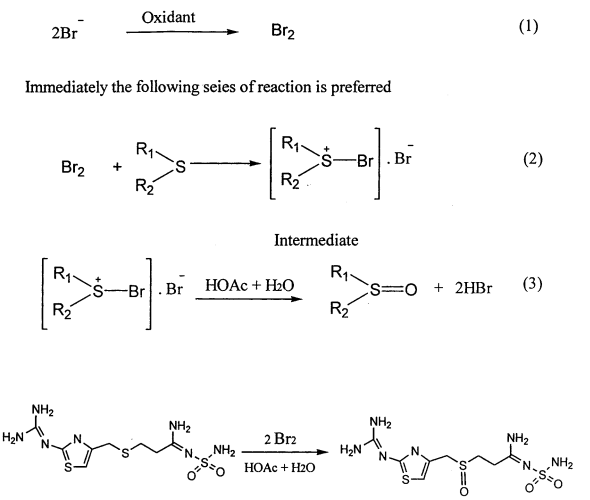
The reproducibility and stability of potential were evaluated over a period of 7 days by determining replication graph ($n = 10$). During this period, the electrode was stored in 1×10^{-3} M drug solution. The detection limit, linear range, response time and selectivity coefficient values were almost constant for the constructed membrane electrode during this period.

3.1.2. Effect of pH

The pH dependence of famotidine is shown in Fig. 3 at two different concentration levels. It was found that the electrode response was independent on pH over the range of 1–5 and the region of pH independence was mildly concentration dependent.

3.1.3. Selectivity of the electrode

The interference effect of different organic and inorganic cations on the electrode response was evaluated. The interference of these compounds



Scheme 1. The oxidation reaction of thioether with lead(IV) in presence of bromine.

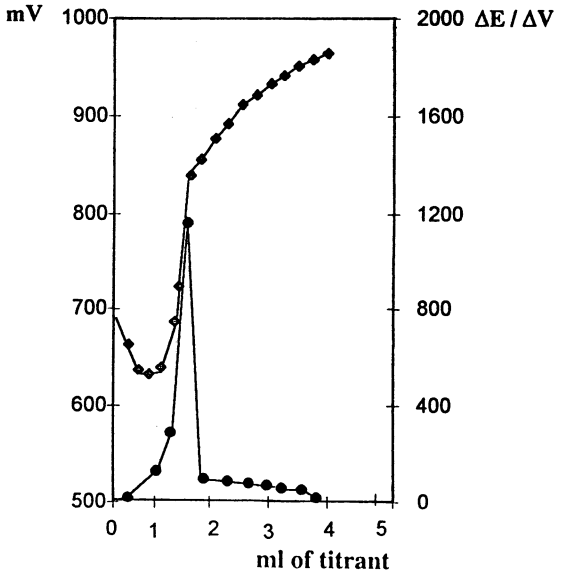


Fig. 4. Potentiometric titration curves of 2.5×10^{-4} M famotidine with 0.1 N lead(IV) acetate in presence of KBr in a ratio 1:100 (●—●), first derivate curve; (◆—◆), titration curve.

was assessed by measuring the selectivity coefficient $K^{\text{pot}}_{\text{famot},j}$ using the separate solution method [20,21] with 10^{-3} M concentration of both the standard famotidine and the interferents. Results obtained are given in Table 1 and reasonable selectivity for famotidine was observed in presence of many interferents. In the most, significant influence on the electrode performance was observed.

3.2. Method 2 (procedure using lead tetra-acetate)

The proposed method is based on the oxidemetric titration of alkyl thioether contained in famotidine with lead(IV) ion in presence of KBr catalyst, which gives rise to an intermediate that can be hydrolysed in an aqueous acidic medium to the sulphoxide. The explanation of this reaction may be as follows (Scheme 1):

The hydrobromic acid liberated is continuously oxidized by the oxidizing agent added during the titration and is immediately used again. Because of the titration curve does not permit a clear differentiation between the potential jump associated with oxidation famotidine and that associated with oxidation of the bromide, it is acceptable, for analytical purposes, to carry out a blank titration with solvent containing the appropriate amount of catalyst and to subtract the corresponding volume of titrant from the subsequent titration.

In agreement with Suchomelova et al. [22], 70% acetic acid was used being the best medium for carrying out the titration. Localization of the end point was accomplished through zero order titration curves of E versus V or through the first derivative curves of $\Delta E/\Delta V$ versus V, where a precise and accurate detection of the end point was obtained, (Fig. 4). The amount of drugs were calculated by the following equation:

$$\text{Amount of drug (mg)} = \frac{MVR}{N},$$

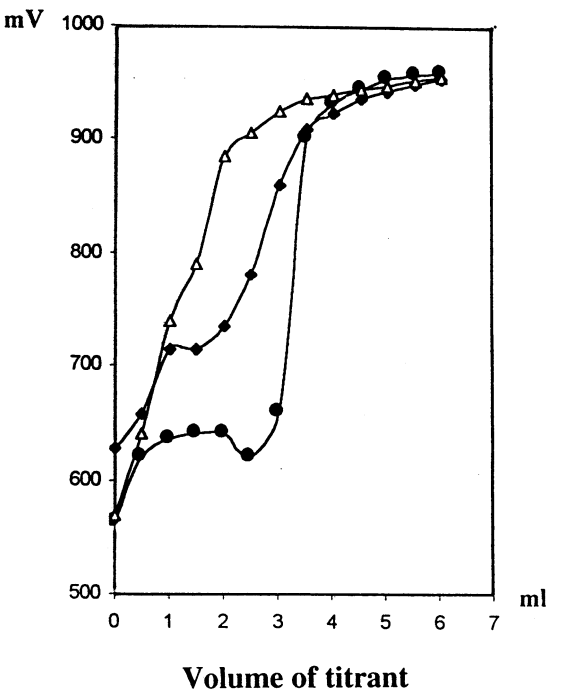


Fig. 5. Potentiometric titration curves of 2.5×10^{-4} M famotidine with 0.1 N lead(IV) acetate in presence of KBr in a ratio 1:100 to the drug in: (●—●), 70% acetic acid medium; (◆—◆), 90% acetic acid medium; and (▽—▽), 99% acetic acid medium.

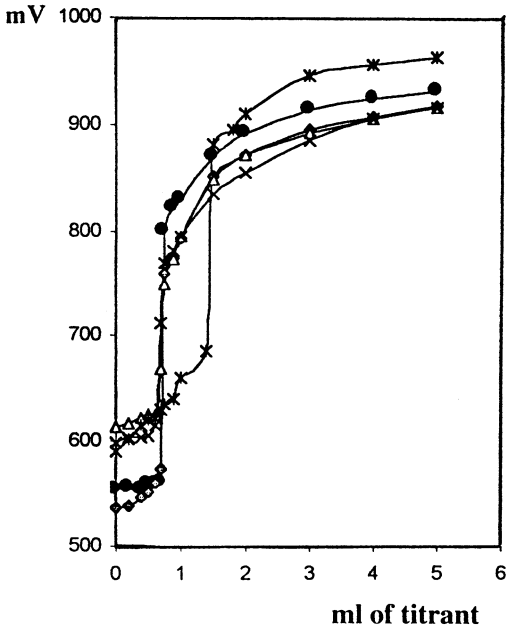


Fig. 6. Potentiometric titration curves of 2.5×10^{-4} M famotidine with 0.1 N lead(IV) acetate: (●—●) in absence of KBr, KBr: drug (◆—◆) 1:100, (▽—▽) 1:50, (x—x) 1:25 and (*—*) 1:1.

where, M is the molecular weight of drug; V, volume of titrant consumed in titration; R, molarity of titrant; and N, number of moles of titrant consumed by 1 mol of drug.

Concerning the parameters affecting the assay of famotidine by the proposed method, it was found that the best medium for titration was 70% acetic acid (Fig. 5) and in presence of KBr in a ratio of 1:100 to famotidine (Fig. 6).

3.3. Quantification, accuracy and precision

The proposed methods were used for direct potentiometric determination of investigated drug, which was performed and calculated from calibration graph. Results obtained were compared with USP23 method [15], Table 3 indicates that the results obtained by the two methods are in good agreement, however, the proposed methods are more selective, simple and less time consuming. In addition, the proposed methods were used for determination of the studied drug in Servipep tablets and results obtained were compared with the official method [15], Table 4 and no significant difference was found between them. The bulk of the excipient in a pharmaceutical tablet, usually consisting of lactose or glucose diluent and corn starch or gelatin binders, does not show any interference. Consequently, the proposed method is recommended for the precise direct potentiometric determination of famotidine in both pure form and pharmaceutical tablets.

4. Conclusion

The proposed methods are advantageous when compared to many reported titrimetric methods in having higher sensitivity. The data given above reveal that the proposed methods are accurate and sensitive (the ISE method > titrimetric method using lead tetra-acetate) with good precision and accuracy. With these methods, one can do the analysis with speed at low cost without

Table 3
Comparative analytical results of the proposed and official USP 23 [15] methods for famotidine in pure form

Items	USP [15]	Proposed	
		ISE method	Titration with lead tetra-acetate method
Mean ± SD	99.91 ± 0.803	99.26 ± 1.115	100.51 ± 1.269
N	7	7	3
V	0.646	1.244	1.612
RSD	0.803	1.123	1.262
t		1.25 (2.179)*	0.922 (2.306)*
F		1.925 (4.28)*	2.495 (5.14)*

* Theoretical values of t and F at $P = 0.05$.

Table 4
Comparative analytical results of the proposed and official USP 23 [15] methods for famotidine in Sevipep tablets (20 mg)

Items	USP [15]	Proposed	
		ISE method	Titration with lead tetra-acetate method
Mean ± SD	99.79 ± 0.928	100.08 ± 0.891	100.72 ± 1.067
N	7	7	4
V	0.861	0.794	1.13
RSD	0.929	0.890	1.059
t		0.596 (2.179)*	1.519 (2.262)*
F		1.084 (4.28)*	1.322 (4.76)*

* Theoretical values of t and F at $P = 0.05$.

losing accuracy. The most important limitation of ISEs is their poor selectivity, especially for compounds of similar structure; this shortcoming does not affect the usefulness in routine analysis and content uniformity determination of famotidine, as it is singly prescribed. The proposed methods can be used as alternative methods to reported ones for the routine determination of famotidine in the pure form and in pharmaceutical tablets depending upon the availability of chemicals and equipment.

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