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Kinetic investigation of Famotidine S-oxidation reaction using potassium caroate. Development and validation of the titrimetric method for the quantitative determination of Famotidine in pure substance and medical preparation

Estudio cinético de la reacción de Famotidina S-oxidación utilizando caroato de potasio. Desarrollo y validación del método titrimétrico para la determinación cuantitativa de Famotidina en sustancia pura y preparación médica

Blazheyevskiy Mykola Yevstahiyovych[1], Serdiukova Yuliia Yuriivna[1]*, Karpova Svitlana Pavlivna[1], Dubenska Liliya Osypivna[2]

1. National University of Pharmacy. Department of Physical and Colloid Chemistry
2. Ivan Franko National University of L'viv, Department of Analytical Chemistry

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Correspondencia
Correspondence

Serdiukova Yuliia Yuriivna
tamadiw@gmail.com

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ABSTRACT

Aims: The kinetic studies of Famotidine (FMT) pure substance and medicinal preparation have been carried out in buffer solutions under second-order conditions at the temperature 293 K for the first time. New titrimetric procedures are described for the FMT determination.

Materials and Methods: FMT pure substance and tablets have been used in analytical reaction with of $KHSO_5$. The kinetic behavior has been studied by the iodometric method in different pH medium.

Results: FMT oxidation reaction has been studied for the S-oxide product under pH=2.0-5.0 and Sulfone product under pH=7.0-8.4. The reaction studied corresponds to the total second order. The Sulfone formation from FMT S-oxide reaction rate constant is in the interval from 14.49 to 32 min^{-1} L mol^{-1}. FMT has been treated with a measured excess of standard potassium caroate in buffer solution with pH 7, after a contact time of 20 min, the residual oxidant back has been determined by the iodometric titration method. The titrimetric method is applicable over 1-10 mg mL^{-1} concentration range and the reaction follows 1:2 (FMT:$KHSO_5$) stoichiometry. The method has been validated for precision, accuracy, linearity, robustness and LOQ. The recovery percent ranged from 99.2 to 100.5%, RSD from 1.09 to 1.70 %, LOQ = 0.03 mg mL^{-1} for pure substance. RSD for tablet formulations has been in the limits from 1.17-2.87 %.

Conclusions: The conditions of FMT S-oxide and Sulfone formation have been optimized. The developed procedures are rapid, simple and inexpensive and could be applied to pharmaceutical preparation.

Keywords: Kinetics, Mechanism, Oxidation, Famotidine, Potassium caroate

RESUMEN

Objetivos: Los estudios cinéticos de substancia y medicamento Famotidina (FMT) han sido realizados en las soluciones amortiguadoras en las condiciones de reacción del segundo orden a temperatura de 293 K. Nuevos métodos titrimétricos están descritos para determinar FMT.

Materiales y métodos: La substancia y los comprimidos FMT han sido usados en la reacción analítica con $KHSO_5$. El comportamiento cinético ha sido estudiado por el método de yodometría en diferentes ambientes de pH.

Resultados: La reacción de oxidación de FMT se estudiaba para el producto del óxido S con pH = 2,0-5,0 y de la sulfona con pH = 7,0-8,4. La reacción a estudiar corresponde al segundo orden general. Las constantes de velocidad de la reacción de la formación de sulfona del óxido S FMT se encuentra en el intervalo de 14,49 a 32 l mol^{-1} min^{-1}. La FMT fue determinada mediante la medición del exceso de solución estándar del caroata de potasio en la solución amortiguadora con pH 7 dentro de 20 minutos desde el inicio de la reacción, luego el oxidante restante fue determinado por el método de titulación yodométrica. El método titrimétrico se aplica en el diapasón de 1-10 mg, la reacción corresponde a la estequiometría 1: 2 (FMT: $KHSO_5$). El método ha sido validado a la precisión, reproducción, linealidad, robustez y LOQ. El

contenido del principio activo es del 99,2 al 100,5%, RSD del 1,09 al 1,70%, LOQ = 0,03 mg / ml para substancia. RSD para comprimidos se encuentra dentro del 1,17 al 2,87%.

Conclusión: Han sido optimizadas las condiciones de formación del óxido S de FMT y sulfona. Los métodos elaborados son rápidos, sencillos y baratos y podrán aplicarse para determinar el fármaco de preparación farmacética.

Palabras claves: cinética, mecanismo, oxidación, famotidina, caroata de potasio

INTRODUCTION

famotidine(FMT),3-[2-(diaminomethyleneamino)thiazol-4ylmethylthio]-N-sulfamoylpropionamidine, is a histamine H2-receptor antagonist (H2-RA) which competitively inhibits the action of histamine on the H2-receptors of parietal cells and thereby reduces the gastric acid secretion under daytime and nocturnal basal conditions. It is easily oxidized and the metabolytes are S-oxides which can be impurities in the medical preparation. The metabolite has no pharmacological activity on gastric acid secretion[1]. It is produced in the form of powder substance and tablets containing 20 or 40 mg of API and other pharmaceutical formulations.

The British Pharmacopoeia[2] recommends a potentiometric nonaqueous method for the determination of FMT using perchloric acid as the titrant, while the USP[3] recommends a similar approach for the determination of FMT in its bulk form, and an HPLC method using a mixture of acetate buffer of pH 6: acetonitrile (93:7) as a mobile phase with UV detection at 275 nm.

An extensive literature survey revealed that FMT has been estimated in pharmaceuticals by spectrophotometry. Spectrophotometric techniques provided practical (less-time-consuming, simple, and more convenient) and significant economic advantages over other methods; therefore, they are a frequent choice for pharmaceutical analyses[4-6]. HPLC methods generally required complex and expensive equipment, provision for use and disposal of solvents, tedious sample preparation procedure, and personal skills in chromatographic techniques[7-11]. Other methods used for FMT quantitative determination belong to capillary electrophoresis[12] and electrochemical methods[13-17]. Some of these methods have enough sensitivity to determine lower concentration of the drug, however, it is always required to develop simple, fast, inexpensive analytical methods that can be readily adopted for routine analysis at relatively low-cost to the different requirements of analytical problems.

Titrimetry is still considered to be very convenient and economical techniques for routine analysis of the drug in pharmaceutical formulations. The FMT content has earlier been determined titrimetrically based on the reaction of drug with chloramine-T[18].

The purpose of the present work is to study kinetics of Famotidine S-oxidation products formation by means of Caro's acid and to develop and validate iodometric procedure for determination of FMT in pure substance and tablet formulation.

MATERIALS AND METHODS

All materials were of the analytical reagent grade, and the solutions were prepared with twice-distilled water.

Famotidine pure substance, Pharmaceutical grade (ac No. FMC/1508003, FM-1507002V 24/08/2015, Nakoda Chemicals Ltd,product-E-P) was used as received. Famotidine preparation, tablets, 20 mg, produced by PJSC «Kyivmedpreparat», Ukraine was used for the research (Certificate No.0010713 24/04/2013). The oxidant was $KHSO_5$, potassium caroate in the form of a triple potassium salt of Caro's acid, $2KHSO_5 \cdot KHSO_4 \cdot K_2SO_4$ (Acros Organics). The choice of the reagent was determined by its rather high oxidative capacity, E^0 = 1.84 V[19], easy availability, and satisfactory solubility in water, and also by sufficiently high stability in the use and storage.

Preparation of standard solutions

Preparation of 0.02 M p*otassium caroate solution.* 0.615 g of $2KHSO_5 \bullet KHSO_4 \bullet K_2SO_4$, was dissolved in twice-distilled water (100 mL). The concentration of potassium caroate was controlled by iodometric titration.

Preparation of 0.005 M Famotidine standard solution. 0.17 g (precise weight) of FMT substance was dissolved 5 mL of 0.1 M HCl solution and after the complete dissolution the volume was brought to the mark with double-distilled water (100 mL).

Preparation of 0.02 M *sodium thiosulfate solution. A* 0.1 mol L^{-1} solution of sodium thiosulfate was prepared from the standard titre fixanal. A 2/10 dilution was made to obtain required concentration.

Preparation of 5 % p*otassium iodine solution*. 5.0 g of potassium iodine was weighted and in 100 mL of distilled water.

Preparation of 0.1 M s*ulfuric acid solution.* The solution was prepared from the standard titre fixanal in a 500 mL volumetric flask.

Preparation of buffer solutions

For pH= 2.30: Dissolve 20.1467 g of $C_6H_8O_7$ H_2O and 1.4604 g of Na_2HPO_4 $2H_20$ in 1000 mL of distilled water.

For pH= 3.60: Dissolve 14.2434 g of $C_6H_8O_7$ H_2O and 11.4696 g of Na_2HPO_4 $2H_20$ in 1000 mL of distilled water.

For pH= 5.00: Dissolve 10.1889 g of $C_6H_8O_7$ H_2O and 18.3443 g of Na_2HPO_4 $2H_20$ in 1000 mL of distilled water.

For pH= 7.00: Dissolve 3.7079 g of $C_6H_8O_7$ H_2O and 29.333 g of Na_2HPO_4 $2H_20$ in 1000 mL of distilled water.

For pH= 8.40: Add 8.00 mL of 0.1 mol L^{-1} HCl solution to 250 mL of 0.2 mol L^{-1} Na_2HPO_4 solution.

Apparatus

pH meter. I-160M Gomel, the Republic of Belarus ESKL-43-07 with glass electrode as indicator was used for pH measurements.

Titration. The titrant volume was measured using a 10 mL microburette with the accuracy of ±0.01 mL.

Voltammetric measurements were carried out on the digital device[20] equipped with personal computer and temperature-controlled three-electrode cell, volume 10 mL. An indicator dropping mercury electrode (DME), a saturated calomel reference electrode and platinum wire auxiliary electrode were used. The dropping mercury electrode employed had the following characteristics: m=5.94 $\cdot 10^{-4}$ g s^{-1}; t_k=10 s in 0.2 M universal buffer solution with open circuit.

IR spectrum of S-oxide prodrug of FMT exhibits characteristic peak at 3401.8 NH stretching 1330.5 cm^{-1} asymmetric SO_2 stretching vibration, 1251.7 cm^{-1} aliphatic CN stretching , 667.2 cm^{-1} S-N stretching vibration.

All the procedures have been performed at room temperature (T=293 K).

Procedure

Studying of Famotidine S-oxidation kinetics. 10,00 mL portion of 0.02 M $KHSO_5$ solution was transferred into 100 mL volumetric flask, 10.00 mL of 0.02 M of NaOH solution and 10 mL of standard FMT solution was added and brought to the mark with corresponding buffer solution, stirred vigorously and left for 1 min. After the addition of FMT solution a stopwatch was switched on. During the first 40 min every 5 min such a procedure has been performed: 10.00 mL aliquot of the mixture obtained was transferred using the pipette into titration flask, 1 mL of 0.1 M sulfuric acid solution and 1 mL of 5 % potassium iodine solution were added. The isolated iodine was titrated by 0.02 M solution of sodium thiosulfate (V, mL).

The control experiment was carried out in the same conditions paralleled (without FMT with the same amount of $KHSO_5$ 0.02 M solution ($V0$, mL)). Each one mL of 0.01 M solution of sodium thiosulfate is equivalent to 0.001350 g of FMT ($C_8H_{15}N_7O_2S_3$) (CAS number 0076824-35-6) (content of FMT is in the limits 98.5-101.5%).

Famotidine pure substance quantitative determination procedure. 10,00 mL portion of 0.02 M $KHSO_5$ solution was transferred into 100 mL volumetric flask, 10.00 mL of 0.02 M of NaOH solution and 5,00 mL; 10,00 mL or 20,00 mL portion of standard FMT solution was added and brought to the mark with pH=7.0 buffer solution, stirred vigorously and left for 1 min. After the addition of FMT solution a stopwatch was switched on. The demand of oxidizing reagent is quantitative and stoichiometric. The time of interaction finishes in 20 min. Further experiment as for *Studying of Famotidine S-oxide kinetics.*

Famotidine tablet formulation quantitative determination procedure. 15 powdered tablets of FMT containing 20 mg of the active substance have been dissolved in 100 mL volumetric flask (see FMT standard solution preparation). The solution obtained has been filtrated through filter paper. Further experiment as for *Famotidine pure substance quantitative determination procedure.* The robustness of the procedure has been checked through the performance of the experiment in two different days.

Method validation

The method was validated according to the guidelines of the International Conference on Harmonization[21].

The Precision and Accuracy on these procedures were investigated with respect to repeatability and determined by performing five repeated analysis of the samples on the same day, under the same experimental conditions.

LOD and LOQ were calculated from regression equation as 3.3 S_0/b and 10 S_0/b respectively, where S_0 and b are standard deviation slope of the calibration curve.

Method comparison. Results obtained in this study were compared to those given in the quality certificates for the pure substance and tablets, i.e. HPLC method.

RESULTS AND DISCUSSION

Kinetic studies were carried out in water medium under second-order conditions with potassium caroate at the temperature 293 K. The reaction was followed by estimating the unreacted Caro's acid as a function of time using the iodometric method. The isolated iodine was titrated against standard sodium thiosulfate solution using starch as indicator.

Metamorphosis of the kinetic curves $1/c$ vs t are given on the Figure 1. The linear dependence reveals the second order reaction (Fig. 1). As it is seen from the plot in the pH value interval 2.3-8.4 the rate of chemical reaction increases.

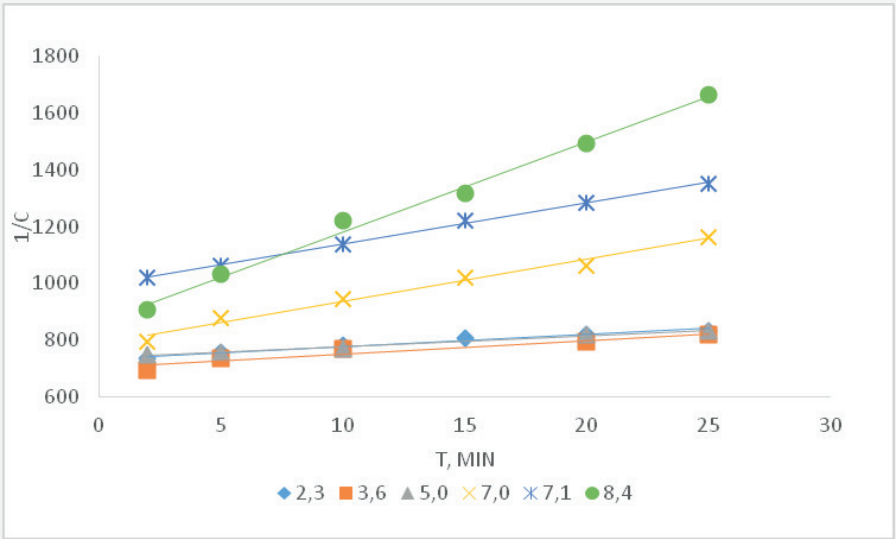

Fig. 1. Dependence of k (1/*c*) on pH. *c*(FMT) = 5×10^{-4} M; *c*(KHSO$_5$) = 2×10^{-4} M

Peroxoacidic titration of standard solutions was carried out to determine the stoichiometry of the reaction.

Stoichiometry of the reaction at the pH 7.0-8.4. From the kinetic curves it is clearly seen that 1 mol of Famotidine is oxidized by 2 mols of KHSO$_5$. The quantitative formation of Sulfone is observed during the time that doesn't exceed 30 min (FMT Sulfone formation from FMT S-oxide).

The formation of Famotidine S-oxide is immediate (during the first minute). The observed rate constants (*kobs*) show the formation of FMT Sulfone. The reaction rate is fast during the first 20 min, but later the reaction slows down (Fig. 2.).

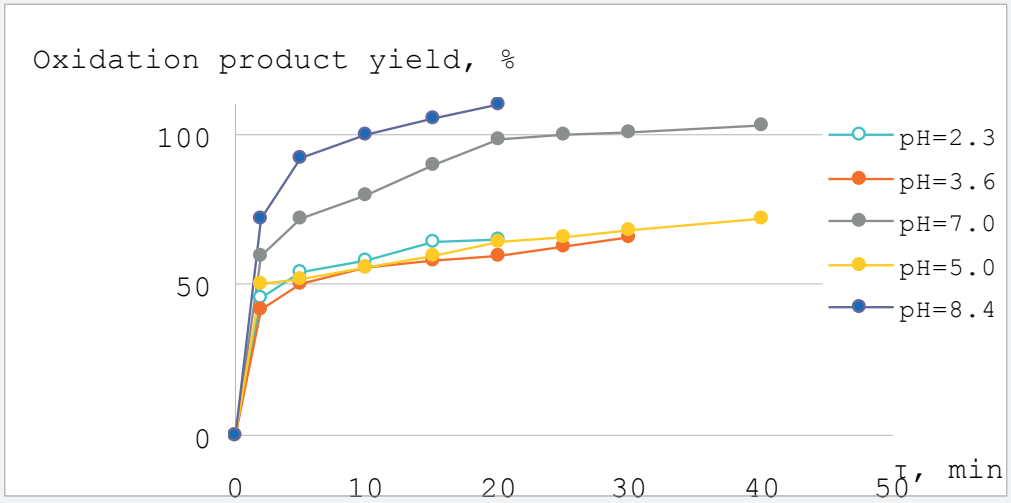

Fig. 2. Dependence of oxidation product yield (%) on time (min). *c*(FMT) = 5×10^{-4} M; *c*(KHSO$_5$) = 2×10^{-4} M

FMT is polarographically nonactive, but it is oxidized by the potassium caroate and is reduced on the mercury drop electrode. The FMT S-oxide is formed in the acidic medium (pH=3-7) at room temperature. Its corresponding peak equals E= -0.6 ÷ -0.8 V. The FMT Sulfone is formed in the basic medium (pH=7-9) and its corresponding peak is in the limit E= -1.4 ÷ 1.5 V. These values can be used as identifications to prove the formation of the corresponding product.

The product was isolated and characterized by IR-spectrum. The shift in S-N stretch occurs in S-oxide prodrug when compared to that of FMT indicates the formation of a S-oxide[22].

The oxidation depth is controlled to a greater extent by the pH of the reaction mixture. Potassium caroate is present in the form of HSO_5^- and SO_5^{2-} ions in solution and they are weak and strong nucelophiles respectively. It is suggested that the reaction proceeds through an nucleophilic attack of the oxidant (HSO_5^-) on the electrophilic site sulfur formed in the first step of the FMT S-oxide reaction (Fig. 3,a) by mince a mechanism involving displacement of terminal oxygen of the peroxide group. A cyclic intermediate undergoes intramolecular rearrangement to give FMT Sulfone (Fig. 3,b) as the product[23].

A hypothetic mechanism scheme based on these observations is proposed on Figure 3:

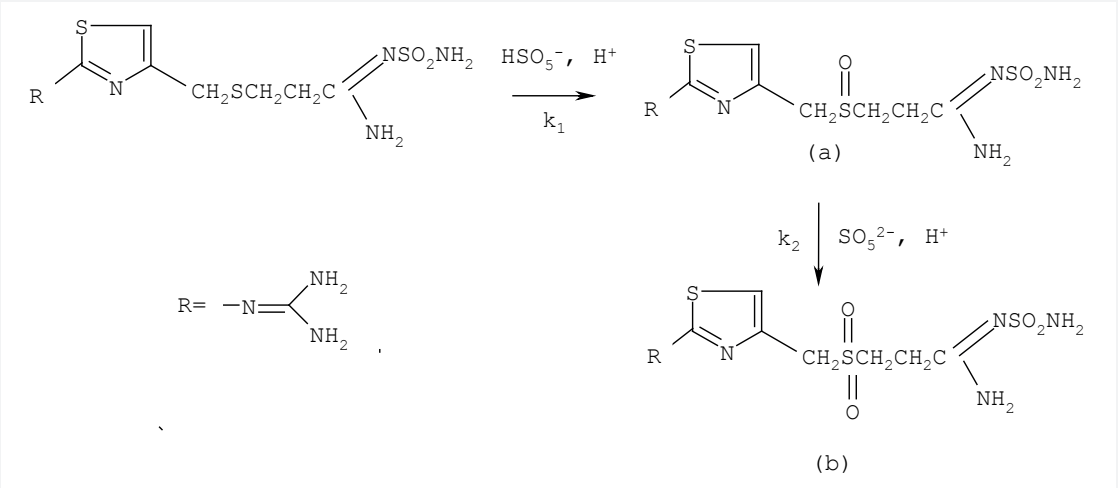

Fig. 3 The scheme of Famotidine S-oxide and Sulfone formation (k_1 » k_2)

The corresponding kinetic equation is following:

$$v = k_1[HSO_5^-][FMT] + k_2[SO_5^{2-}][FMTO]$$

This, in particular, points to a linear dependence of the observed reaction rate constant on the molar fraction of the dianion of the Caro's acid.

The fact that the maximum rate (second order) falls at pH value equal to pK_2 value (about 9.4) of Caro's acid[24] explains that at this pH value the highest rate of spontaneous decomposition of Caro's acid (attack of monoanion on dianion) is observed. That is why such pH of the medium should be avoided. Indeed, the overexcess of the oxidation reagent is observed at the pH=8.4. In the research work of Pylypchuk and others have studied the stability of diluted solution of Caro's acid depending on the temperature and pH values. In the conclusion optimal pH 3-4 have been recommended as the most stable at room temperature[25]. So, taking into account all the mentioned above and the results obtained during the experiment (Fig.4) the optimal pH for FMT Sulfone formation is 7.0. At this pH value sulfone derivates are formed with satisfactory rate (20 min) plus uncontrolled decomposition of the oxidizing agent in an auxiliary reaction.

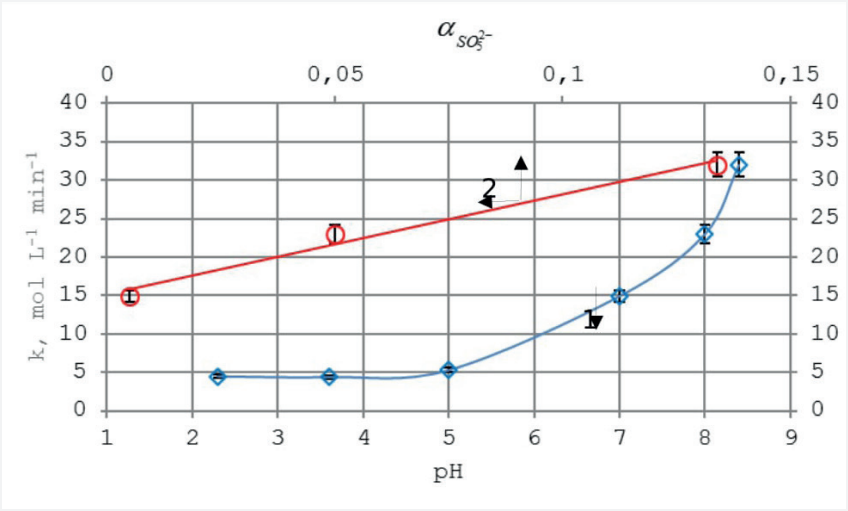

Fig. 4. The dependence of the observed reaction rate constant on pH (1) and on the molar fraction of the dianion of the Caro's acid (2) (r=0.990). c**(FMT) = 5×10^{-4} M;** c**(KHSO$_5$) = 2×10^{-4} M**

The proposed method was validated statistically for Famotidine pure substance and medical preparation. The iodometric back titration method equation was used for the calculations. The results are shown in the Table 1.

Table. 1. Results of Famotidine pure substance accuracy and precision calculation

Added, M 10^3	Found, M 10^3	Mean, M 10^3	Recovery, %	RSD, %	δ*, %
2.50	2.45	2.48	99.20	1.70	0.80
	2.50				
	2.47				
	2.55				
	2.45				
5.00	5.10	5.02	100.40	1.53	0.40
	4.96				
	4.96				
	5.15				
	5.10				
10.00	6.97	10.05	100.50	1.09	0.50
	6.97				
	7.10				
	7.19				
	6.97				

***Calculated using the certificate data obtained by the HPLC method**

The method is linear in a wide range: 1-10 mg mL^{-1} with the equation Y = (0.9954±0.13)X, R=0.999. The calculated LOD = 0.01 mg mL^{-1} and LOQ = 0.03 mg mL^{-1} show high sensitivity of the procedure proposed.

The procedure was approbated for the tablet form. The results have been calculated by the method of standards corrected by the average tablet mass. The data obtained are shown in the Table 2.

Table. 2. Results of Famotidine tablets accuracy, precision and robustness calculation

Level	FMT, tablet formulations, mg					
	Day 1			Day 2		
	41.6	20.8	10.4	41.6	20.8	10.4
1	39.9	21.1	10.9	41.7	20.9	10.2
2	39.9	20.9	10.9	41.7	20.4	10.2
3	41.7	21.3	10.4	41.7	21.1	10.4
4	42.6	20.4	10.4	42.6	21.3	10.4
5	42.6	21.1	10.2	40.8	21.3	10.9
Mean, mg	42.06	20.96	10.56	41.70	21.00	10.43
RSD, %	1.17	1.64	2.87	1.53	1.78	2.66
δ*, %	1.11	0.77	1.54	0.24	0.96	0.29

***Calculated using the certificate data obtained by the HPLC method**

CONCLUSIONS

The kinetics of Famotidine S-oxide and Sulfone formation by means of potassium caroate have been studied. Optimal conditions for the Famotidine Sulfone formation have been proposed (pH=7.0, t=20 min).

Titrimetric method is described for the determination of Famotidine in pure substance and tablet formulations using potassium caroate as oxidimetric agent. The procedure proposed is linear for pure substance in the interval 1-10 mg mL^{-1} and r=0.999 with the recovery percent ranged from 99.2 to 100.5%, RSD from 1.09 to 1.70 % and LOQ = 0.03 mg mL^{-1} for pure substance.

The validation has been performed for tablet formulations with good results obtained. RSD for tablet formulations has been in the limits from 1.17-2.87 % (δ = -0.24÷-1.54 %).

The proposed procedure is demonstrated to be simple and cost-effective compared to many reported methods including the official ones.

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