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Development and Validation of Spectrophotometric and Pre-column Derivatization HPLC Method for Determination of Famotidine in Pharmaceuticals by Reaction with Sodium Nitroprusside; Application to Combined Tablets

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Abstract

Spectrophotometric and HPLC methods for estimation of famotidine in pharmaceutical formulations through derivatization with sodium nitroprusside were developed. The spectrophotometric method is based on measuring the red color formed after the reaction with sodium nitroprusside at 498 nm. The formed product was further determined by HPLC method using C_{18} column, mobile phase composed of methanol and 0.05 M phosphate buffer (30:70, v/v) with apparent pH 4, The UV detection was at 498 nm. Both methods were linear covering concentrations of 20-500 µg/mL. The selectivity and the simplicity of the methods allow the successful estimation of famotidine in its pharmaceuticals and in its combined tablets with ibuprofen, domperidone, paracetamol and diclofenac without interferance.

Keywords: Famotidine, Derivatization, Sodium nitroprusside

Introduction

Famotidine (FMT) is 3-[2-[(aminoiminomethyl)amino]-4-thiazolyl]methyl]thio]-N-(aminosulfonyl) propanimidamide (Figure 1) [1]. FMT is a histamine H_2-antagonist, usually administred for gastric, duodenal ulceration and gastro-esophageal reflux disease [2]. Different methods were used for the quantification of FMT in its dosage forms and biological fluids like: spectrophotometry [3-9] spectrofluorimetry [10,11], voltammetry [12,13], TLC [14,15], HPLC [16-25] and capillary electrophoresis [16,26-28]. U.S.P. recommended a potentiometric non aqueous titrimetric method for the determination of FMT in its bulk form and chromatographic method for its determination in tablets [29] FMT has been derivatized previously by sodium nitroprusside by a spectrophotometric method but this method lacks the application of the method of for the determination of famotidine in ampoules and even in presence of co-formulated drugs of ibuprofen and domperidone [30].

Application of derivatization is one of famous tool for analysis, especially using chromatography, and reactions were used in developing methods allow quantitation several classes of compounds. May be due to enhancement the analyte recovery, separation, detection and identification of different compounds [31].

To the best of our knowledge, the proposed HPLC method is considered as the first HPLC using a derivatization reaction with UV detection has been reported for famotidine determination. Furthermore, it is a selective method for the estimation of FMT either alone or even in presence of co-formulated drugs like ibuprofen, domperidone, diclofenac and paracetamol without interference.

Experiment

Apparatus

- A Shimadzu recording Spectrophotometer (UV-1601, P/N 206-67001) with 1-cm matched cells was used.
- HPLC experiments were performed by a Merck Hitachi L-7100 Chromatograph, Rheodyne injector valve with a 20 µL loop and a detector of L-7400 UV (Darmstadt, Germany) integrator of a Merck Hitachi D-7500, and a degasser of Merck L-7612 solvent degasser.
- For pH measurements using Consort NV P-901 pH–Meter.

Materials or reagents

Famotidine (FMT) was obtained from Memphis Chemical Company, Cairo, Egypt. Its purity according to U.S.P was found to be 98.81%, 1% aqueous solution of sodium nitroprusside (El-Goumhoria Co.,Cairo, Egypt), was prepared. 1 M solution of each of sodium hydroxide and hydrochloric acid (El-Nasr Chem. Co., Cairo, Egypt), were prepared. Mono basic hydrogen phosphate was obtained from El Nasr Chem. Co. (Cairo, Egypt). Methanol and acetonitrile were purchased from Sigma- Aldrich Company Germany). Antodine®

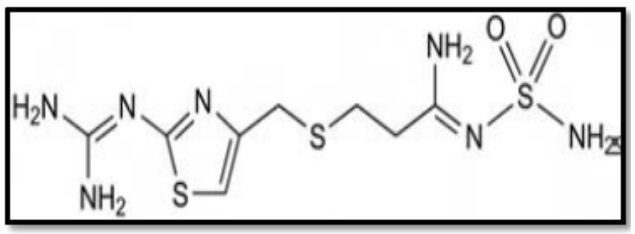

Figure 1: Structure of Famotidine.

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ampoules (Batch#22298) of 20 mg famotidine/ampoule, and Antodine® tablets (Batch#3728), of 20 mg famotidine/tablet, produced by Amoun Pharmaceutical Company, El-Obour City, Cairo, Egypt. Servipep® tablets (Batch#050), of 40 mg famotidine/tablet, Novartis Pharma Company, Cairo, Egypt. Laboratory prepared tablets composed of 26.6 mg famotidine, 800 mg ibuprofen with 15 mg lactose, 10 mg magnesium stearate, 20 mg talc and 15 mg maize starch per tablet. Laboratory prepared tablets composed of 20 mg famotidine, 10 mg domperidone with 15 mg lactose, 10 mg magnesium stearate, 20 mg talc and 15 mg maize starch per tablet.

Chromatographic conditions

The chromatographic conditions applied using Waters Symmetry® C_{18} column (250 mm×4.6 mm i.e., 5-µm particle size). Mobile phase: consists of methanol and 0.05 M sodium dihydrogen phosphate (30:70, v/v) adjusted to apparent pH 4 with flow rate 1.0 mL/min. The separation was operated at ambient temperature and the detection wavelength of 498 nm.

Standard stock and working solutions

Famotidine stock solution of 100 mg in 25 mL methanol in volumetric flask (4000 µg/mL) was dissolved. Further dilution with methanol was used to get the required working solution. The solution was kept in refrigerator.

Procedures

Calibration graphs determination

For Method I: A liquots of the standard solution of FMT was determined using a series of 10.0 mL volumetric flasks covering the concentrations of 20-500 µg/mL, 1 mL of 1 N NaOH was added followed by 1.2 mL of sodium nitroprusside solution with shaking. After 8 min, add 1 mL of 1 N HCl and complete to the mark with water. The absorbance versus the final concentration of the drug in µg/mL was plotted. Alternatively, the corresponding regression equation was derived.

For Method II: Accurately measured aliquots of the standard solution of FMT was transferred into a series of 10.0 mL volumetric flasks so that the final concentration was in the range of 20-500 µg/mL, 1 mL of 1 N NaOH was added 1.5 mL with shaking. After 8 min, 1 mL of 1 N HCl was added and the solution was completed to the mark with mobile phase, and analysed under optimum chromatographic conditions. The peak area versus the final concentration of the drug in µg/mL was plotted. Alternatively, the corresponding regression equation was derived.

Analysis of FMT in pharmaceutical formulations

Tablets: 10 tablets of 20 mg or 40 mg of FMT were pulverized and weights of 20 mg and 40 mg were transferred into a 100 mL volumetric flask and about 50 mL of methanol were added, sonicated for 30 min, completed to the mark with methanol and filtered. Further dilution with methanol was used to get working solution. Apply the general procedure as described under "construction of calibration graphs". The nominal content of tablets was calculated plotted calibration graph or using the corresponding regression equation.

Ampoules: The contents of five ampoules were mixed well, aliquot volumes equivalent to 50 mg of FMT were transferred into a 100 mL volumetric flask, completed to the mark with methanol. Further dilution with methanol was used to get working solution, apply the general procedure as described under "construction of calibration graphs of FMT". The nominal content was calculated from plotted calibration graph or using the corresponding regression equation.

Combined tablets of famotidine and ibuprofen: An accurately weighed quantity of the mixed contents of five prepared tablets equivalent to 26.6 mg of FMT and 800 mg of ibuprofen was transferred into 50 mL volumetric flask and about 30 mL of methanol were added. The contents of the flask were sonicated for 30 min, completed to the mark with methanol and filtered. Further dilution with methanol was used to get working solution, apply the general procedure as described under "construction of calibration graphs of FMT". The nominal content was calculated either from a previously plotted calibration graph or using the corresponding regression equation.

Combined tablets of famotidine and domperidone: An accurately weighed quantity of the mixed contents of five prepared tablets equivalent to 20 mg of FMT and 10 mg of domperidone was transferred into 50 mL volumetric flask and about 30 mL of methanol were added. The contents of the flask were sonicated for 30 min, completed to the mark with methanol and filtered. Further dilution with methanol was used to get working solution, apply the general procedure as described under "construction of calibration graphs of FMT". The nominal content was calculated either from a previously plotted calibration graph or using the corresponding regression equation.

Combined tablets of FMT, paracetamol and diclofenac: An accurately weighed quantity of the mixed contents of 10 prepared tablets equivalent to 20 mg of FMT, 500 mg of PRC and 50 mg of DCF was transferred into a 100 mL volumetric flask and about 50 mL of methanol were added. Sonication for 30 min, completed to the mark with methanol and filtered. Further dilution with methanol was used to get working solution to be assayed by subjecting to the general procedure of (method II) as there is some interference from paracetamol in (method I). The nominal content of each drug was calculated either from a previously plotted calibration graph or using the corresponding regression equation.

Results and Discussion

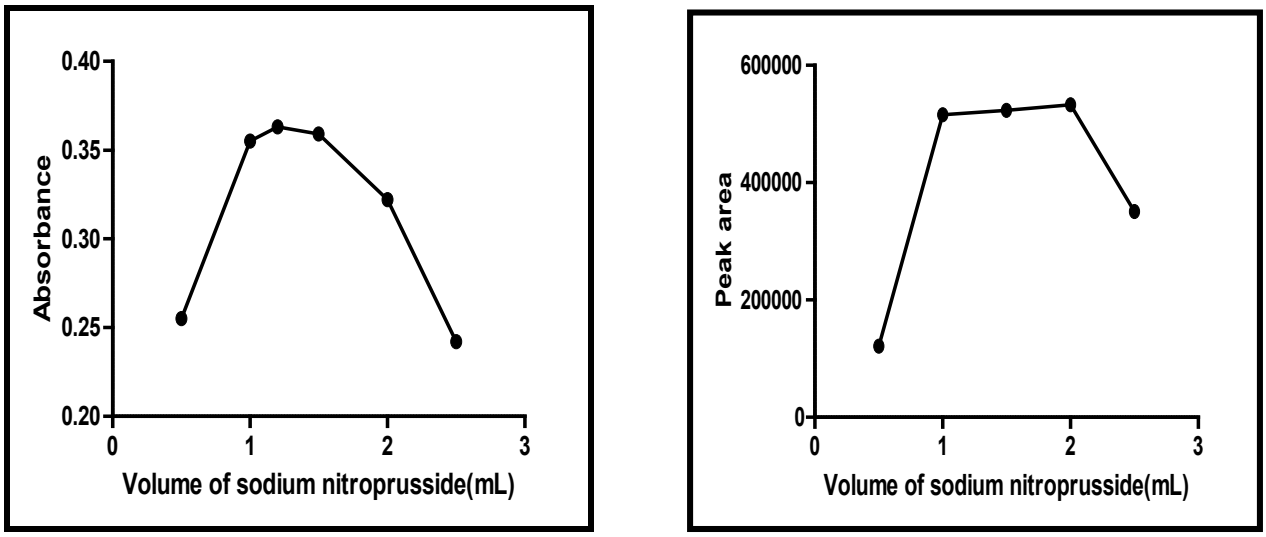
Optimization of derivatization conditions

Sodium nitroprusside reacts with FMT in alkaline medium to form a red colored complex has absorption maximum at 498 nm as shown in Figure 2. The mechanism of the reaction was postulated (Scheme 1).

For the evaluation of optimal derivatization conditions for FMT, Several factors influencing the absorbance and the peak area of the drug after derivatization reaction were carefully studied, including the order of addition, volume of sodium nitroprusside, concentration of NaOH and HCl and the reaction time.

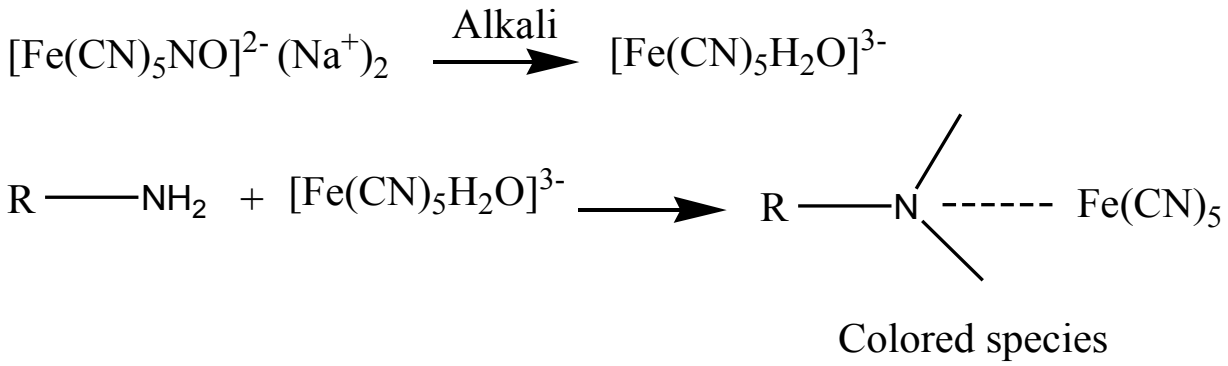
The order of addition: The order of addition of the reagents is first that sodium nitroprusside should be treated with FMT in alkaline medium then HCl is then added to make the solution acidic with the highest absorbance or peak area were obtained.

Effect of sodium nitroprusside volume: Different volumes of sodium nitroprusside were added ranging from 0.5-2 mL to ensure



(A) Reagent blank
(B) The reaction product of 400 µg/mL of FMT with sodium nitroprusside

Figure 2: Absorption spectra of the reaction of FMT with sodium nitroprusside where.



Scheme 1: Proposal mechanism for the reaction of famotidine with sodium nitroprusside.

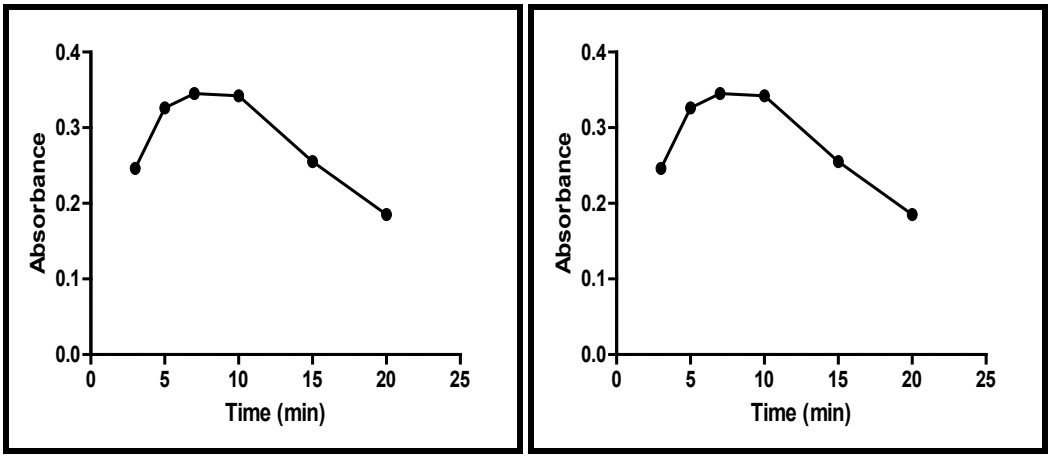
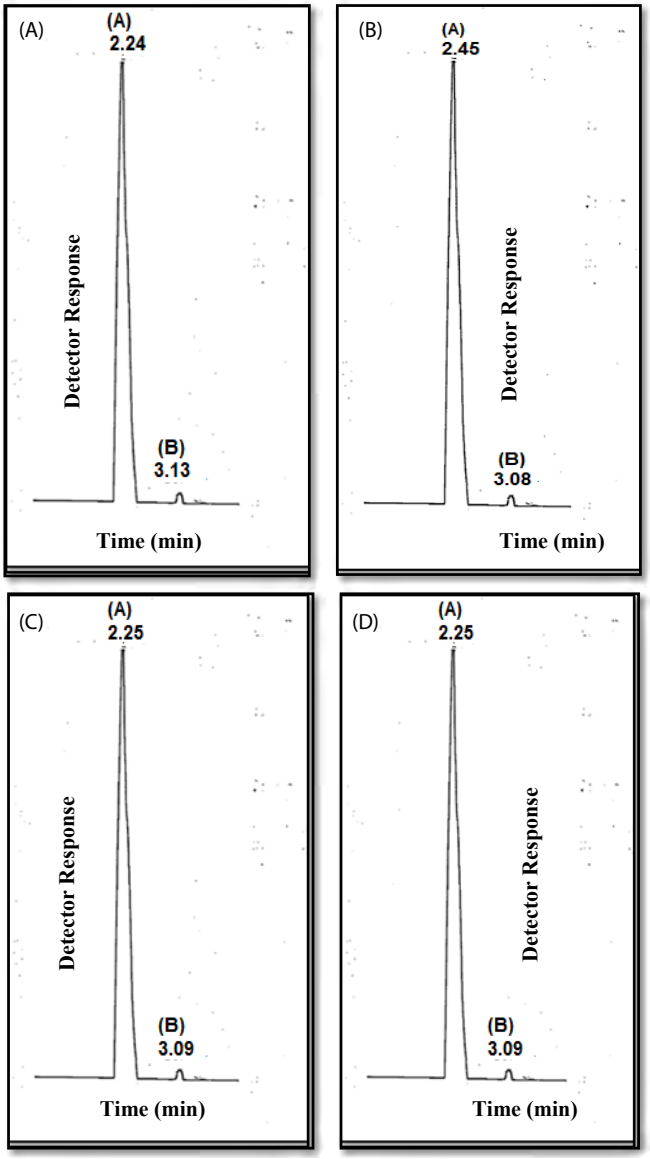


Figure 3: Effect of volume of sodium nitroprusside on the reaction with FMT (200 µg/mL).

complete derivatization with FMT. The optimized volume was found to be 1.2 mL (For method I) and 1.5 mL (For method II) as maximum absorbance or peak area value of FMT derivative was achieved (Figure 3).

Concentration of NaOH and HCl: Different volumes of both NaOH and HCl were tried. It was found that increasing the volume of NaOH than HCl volume, no red color formed. So, 1 ml of each was adequate giving the maximum absorbance or peak area.

Effect of the reaction time: The reaction time was also studied. The peak area was measured after different time of the derivatization reaction from 5-20 min. For method both methods, 8 min was adequate because after which there is no increase in the absorbance or the peak area (Figure 4).



(A) 400 µg/mL of FMT derivatized by sodium nitroprusside
(B) 400 µg/mL of FMT tablets after derivatization by sodium nitroprusside
(C) 400 µg/mL of FMT ampoules after derivatization by sodium nitroprusside
(D) Combined tablets of 400 µg/mL of FMT after derivatization by sodium nitroprusside in presence of ibuprofen or domperidone or paracetamol or diclofenac

Figure 4: Typical chromatogram under described chromatographic conditions.

Optimization of chromatographic conditions for the HPLC method

Different experimental trials were studied to obtain Well-defined symmetrical peak that can be summarized as follows:

Choice of column: Two columns were tried including, C_8 column (250 × 4.6 mmi.d., 5 µm particle size) and Waters symmetry® C_{18} column (250 mm×4.6 mm i.e., 5 µm-particle size). Experimental studies revealed that, upon using C_{18} column unsymmetrical and tailed peak was obtained. So, C_{18}column was used throughout the work showing well defined symmetrical peak.

Choice of detection wavelength: The UV detection of the reaction product gives maximum absorbance at 498 nm with the formation of a red color as shown in Figure 2. So, 498 nm was used as the detection wavelength.

Mobile phase composition: Several modifications in the mobile phase composition were performed. These modifications included; the change of pH, mobile phase ratio, mobile phase composition, buffer molarity and the flow rate. The results obtained are shown in Table 1.

Apparent pH of the mobile phase: Upon changing the apparent pH of the mobile phase over the range 3-4.5, it was found that by decreasing the pH less than 3.5 gives unsymmetrical peak. So pH 4 was used throughout the work giving well defined and symmetrical peak.

Mobile phase ratio and composition: Different ratios of methanol and sodium dihydrogen phosphate were tried. The ratio of (50:50, v/v) causes the formation of a forked peak with peak broadening. While by increasing the ratio of sodium dihydrogen phosphate to methanol decreases the peak broadening. So, ratio (30:70, v/v) of methanol to sodium dihydrogen phosphate was used giving good symmetrical peak in a reasonable retention time as shown in Table 1. The replacement of methanol by acetonitrile causes the formation of a broad peak while, using water instead of buffer causes the retention of the peak for more than 20 min, So methanol and sodium dihydrogen phosphate were most suitable.

Buffer molarity: The influence of sodium dihydrogen phosphate molarity on the peak area was studied using concentration of 0.01-0.05 M of sodium dihydrogen phosphate (Table 1). By increasing the molarity to 0.1 M of sodium dihydrogen phosphate, the peak was not sharp and unsymmetrical. So, the concentration of 0.05 M was used throughout the work.

Flow rate: The effect of flow rate on the separation of peak of the studied compound was studied in the range 0.8-1.2 mL/min, flow rate of 1.0 mL/min was optimal one regarding good separation in a reasonable time as shown in Figure 3.

The Method Validity: The validity of the methods were checked by testing linearity and range, LOD, LOQ, accuracy, repeatability, precision and selectivity according to ICH recommendations [32].

Linearity and range: The estimation of linearity of the proposed methods were achieved by construction of the calibration curves. The absorbance or peak area against the concentration in µg/mL of FMT was obtained, in concentration range cited in Table 2. Linear regressions were calculated using the following equations:

A = 0.1336 + 0.0012 C (r = 0.9999) for method I

Parameter		No. of theoretical plates(N)
pH of mobile phase	3	1180
	3.5	1213
	4	1260
	4.5	1245
Mobile phase ratio of methanol:sodium dihydrogen phosphate(v/v)	50:50	960
	40:60	1200
	30:70	1475
	20:80	1150
Conc. of phosphate buffer (M)	0.02	1290
	0.03	1450
	0.04	1660
	0.05	1590
Effect of flow rate (mL/min)	0.8	1298
	1.0	1386
	1.2	1420

*Where: Number of theoretical plates: (N) = $5.54(\frac{t_R}{W_{h/2}})^2$

Table 1: Optimization of the chromatographic conditions for determination of FMT by the proposed HPLC method.

Parameters	Method I	Method II
Linearity and range (µg/mL)	20-500	20-500
LOD (µg/mL)	5.51	6.34
LOQ (µg/mL)	16.70	19.22
Correlation coefficient (r)	0.9999	0.9999
Slope	1.2 x10^{-3}	1098.94
Intercept	0.1336	4717.49
$S_{y/x}$,S.D. of the residuals	3.2 x10^{-3}	3350.48
S_a ,S.D. of the intercept	2 x10^{-3}	2112.42
S_b ,S.D. of the slope	1x10^{-4}	7.60

Table 2: Analytical performance data for the determination of FMT by the proposed spectrophotometric and HPLC method.

P = 4717.49 + 1098.94 C (r = 0.9999) for method II

Where: A is the absorbance, P is the peak area, C is the concentration of the drug in µg/mL and r is the correlation coefficient.

Statistical analysis [33] revealed good values of correlation coefficient (r), standard deviation of residuals (Sy/x), of intercept (Sa), of slope (Sb), small value of the percentage relative standard deviation and the percentage relative error (Table 2). These data proved the linearity of the calibration graph.

Detection limit (LOD) and quantitation limit (LOQ): LOD is defined as the minimum level at which the analyte can be reliably detected [32]. It was found to be 5.51 µg/mL and 6.34 µg/mL for method I and II respectively. While LOQ is the lowest concentration that can be measured according to ICH Q2R1 recommendations[32] below which the calibration graph is nonlinear. It was found to be 16.70 µg/mL 19.22 µg/mL for method I and II respectively, Where:

LOD=3.3 Sa /b LOQ=10 Sa /b

Sa=standard deviation of the intercept of the calibration curve and b= slope of the calibration graph (Table 2).

Accuracy and precision

The accuracy was determined by comparison of the assay results obtained with that of the comparison method [29]. Student's t-test and variance ratio F-test [33] revealed no significant difference between results of the proposed and the comparison methods (Table 3). The precision for assay were determined by repeatability (inter-day) and intermediate precision (intra-day) for the proposed methods.

Intraday precision: Three concentrations of FMT were analysed on three successive times. The results showed good precision within day. The results are abridged in Table 4.

Interday precision: Three concentrations of FMT were analysed on three successive days. The results are cited in Table 4. The small value of relative standard deviations of indicating high repeatability and intermediate precision of the proposed methods.

Robustness: The robustness was checked by changing of such parameters; volume of the reagent and reaction time both methods. While for method II, pH of the mobile phase (4±0.1), mobile phase ratio (30:70 ±2%) and buffer molarity [0.05±0.005 M]. These changes didn't affect the peak area of the studied drug.

Selectivity: The proposed methods were selective for the evaluation of FMT in different dosage forms as well as in the presence of the co-formulated drugs of Ibuprofen, Domperidone Paracetamol and Diclofenac without interference, the results were summarized in Table 5.

Application of the proposed methods for estimation of FMT in different dosage forms

The proposed methods were successfully applied to the determination of FMT in its dosage forms. Moreover, the methods were also applied to the estimation of the drug in presence of ibuprofen, domperidone, paracetamol and diclofenac. The results are in good agreement with those obtained using the comparison method [29] Statistical analysis of the results were a good guide revealed that there is no difference between the results of the proposed and the comparison methods.

Conclusion

The developed spectrophotometric and HPLC method for determination of FMT were developed with the advantages of being reliable, simple and rapid. The methods were applied for the analysis

Famotidine	Conc. taken (µg/mL)	Method I	Method II	Official method[29] % Found
		% Found	% Found	
	20 50 100 200 400 500	97.50 102.33 100.33 98.00 100.29 99.40	101.31 98.72 102.04 98.25 100.99 99.57	99.88 100.30 98.56
$\bar{X}$±SD		99.64 ±1.76	100.15±1.52	99.58± 0.91
t-test		0.05 (2.36)*	0.58 (2.36)*	
F-test		3.75 (19.29)*	2.81 (19.29)*	

* Figures between parentheses are the tabulated t and F values at p =0.05[33]
* Each result is the average of three separate determinations.
Table 3: Application of the proposed methods for the analysis of FMT in pure form.

	Intra-day precision			Inter-day precision		
	Conc.added (µg/mL)	Method I	Method II	Conc.added (µg/mL)	Method I	Method II
		% Found	% Found		% Found	% Found
FMT	100	98.56	100.71	100	100.22	99.55
	200	99.21	99.28	200	98.13	98.86
	400	98.23	99.95	400	99.35	99.20
$\bar{X}$ ±S.D.		98.67±0.50	99.98±0.72		99.23±1.05	99.20±0.35
%R.S.D.		0.51	0.72		1.06	0.35
%Error		0.29	0.41		0.61	0.20

N. B. Each result is the average of three separate determinations.

Table 4: Accuracy and precision data for the determination of FMT by the proposed methods.

Preparation	Proposed method			Official method[29]
	Conc.taken (µg/mL)	Method I	Method II	
		% Found	% Found	% Found
Antodine® tablets (20 mg FMT/tab.)	100 200 400	98.22 99.65 100.35	99.65 98.25 101.70	99.42 98.21 99.67
$\bar{X}$ ±SD t F		99.41±1.09 0.39 (2.77)* 1.93 (19)*	99.87±1.74 0.69 (2.77)* 4.93 (19)*	99.10±0.78
Antodine® ampoules (20 mg FMT/amp.)	100 200 400	101.15 100.25 98.12	99.95 100.30 98.75	98.35 101.23 100.75
$\bar{X}$ ±SD t F		99.84±1.56 0.21 (2.77)* 1.01(19.0)*	99.67±0.81 0.44 (2.77)* 3.60 (19.0)*	100.11±1.54
Servipep® tablets (40 mg FMT/tab.)	100 200 400	99.65 98.67 102.20	101.95 100.06 99.85	99.65 100.55 100.65
$\bar{X}$ ± SD t F		100.17±1.82 0.1 (2.77)* 10.94 (19.0)*	100.62±1.16 0.45 (2.77)* 4.41 (19.0)*	100.28±0.55
Laboratory Prepared tablets (26.6 mg FMT+800 mg ibuprofen/tab.)	50 100 200	100.36 98.33 102.05	99.95 98.88 99.41	98.56 100.45 98.68
$\bar{X}$ ±SD t F		100.25±1.86 0.82 (2.77)* 3.09 (19.0)*	99.41±0.54 0.26 (2.77)* 3.91 (19.0)*	99.23±1.06
Laboratory Prepared tablets (20 mg FMT+10 mg domperidone/tab.)	50 100 200	99.13 101.38 98.86	98.55 98.95 100.66	99.75 100.23 98.60
$\bar{X}$ ± SD t F		99.79±1.38 0.28 (2.77)* 2.72 (19.0)*	99.39±1.12 0.17 (2.77)* 1.79 (19.0)*	99.53±0.84
Laboratory Prepared tablets (20 mg FMT+500 mg PRC+50 mg DCF/ tab.)	20 25 30		98.86 101.88 99.33	100.36 99.48 100.48
$\bar{X}$ ± SD t F			100.02±1.63 2.13 (2.77)* 8.85 (19.0)*	100.11±0.55

Note: Each result is the average of three separate assays.

*Values between brackets are the tabulated t and F values at p=0.05[33]

*Nominal content of famotidine in Antodine® tablets = 19.88 mg/tablet (for method I) and 19.97 mg/tablet (for method II).

*Nominal content of famotidine in Antodine® ampoules = 19.96 mg/ ampoule (for method I) and 19.93 mg/ampoule (for method II).

*Nominal content of famotidine in Servipep® tablets = 40.06 mg/tablet (for method I) and 40.24 mg/tablet (for method II).

*Nominal content of famotidine in laboratory prepared tablets with ibuprofen = 26.66 mg/tablet (for method I) and 26.44 mg/tablet (for method II)

*Nominal content of famotidine in laboratory prepared tablets with domperidone = 19.95 mg/tablet (for method I) and 19.87 mg/tablet (for method II)

*Nominal content of famotidine in laboratory prepared tablets with paracetamol and diclofenac = 20.004 mg/tablet (for method II).

Table 5: Application of the proposed methods to the determination of FMT in pharmaceutical formulations.

of FMT in its raw material, tablets, and ampoules as well as in its combined tablets with ibuprofen, domperidone, paracetamol and diclofenac without interference, the results were with good agreement with comparison method. The good validation criteria of the proposed methods allow its applicability in quality control laboratories.

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