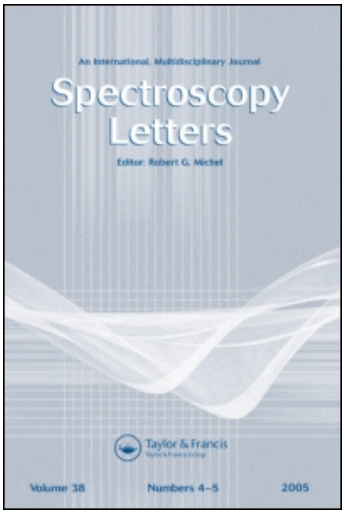

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DIFFERENT SPECTROPHOTOMETRIC METHODS FOR THE DETERMINATION OF CIMETIDINE, RANITIDINE HYDROCHLORIDE, AND FAMOTIDINE

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ABSTRACT

In this work three different spectrophotometric methods were established for the determination of cimetidine (I), ranitidine hydrochloride (II) and famotidine (III).

The first one is a colorimetric method, it was applied for the determination of the three drugs by using sodium nitroprusside as a color reagent to produce a red colored complexes. In this method, the zero order spectrum ^{0}D was used for the determination of drug (III) at $\lambda = 500$ nm while the first derivative spectra ^{1}D were used for the determination of drug (I) and (II) at their corresponding wave lengths 523 and 510 nm and $\Delta\lambda = 4$ nm.

The method can be considered as a stability indicating method for the determination of the three drugs in the

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presence of their induced hydrogen peroxide oxidative degradates. Beer's law was obeyed in the concentration range of 25–150 $\mu g \cdot mL^{-1}$ for (I) and 50–500 $\mu g \cdot mL^{-1}$ for (II) and (III) with mean percentage recoveries of 100.27 ± 0.697, 99.79 ± 0.465 and 99.15 ± 0.687, respectively.

The second method is a simple colorimetric method, it was applied for the determination of drug (III). Where, 3-Methyl-2-benzo-thiazolinone hydrazone (MBTH) was used as a color reagent. It reacts with the drug to produce a bluish violet color, having two maxima at 536 and 620 nm. The percentage recoveries were 99.73 ± 1.048 and 99.94 ± 0.887, respectively within the concentration range of 20–120 $\mu g \cdot mL^{-1}$.

The third one is a spectrophotometric method via a complex formation reaction by using cobalt II. A colorless complex was developed having λ_{max} at 319 nm with a ratio of 1:1 and a stability constant logarithm of 5.49. The percentage recovery was 99.84 ± 0.858 within a concentration range of 10–60 $\mu g \cdot mL^{-1}$.

The statistical comparison with the BP official methods[1] and the assay validation for the three proposed methods has been applied. The results obtained showed that they could be used for the determination of the three drugs in pure and dosage forms.

Key Words: Spectrophotometry; Cimetidine; Famotidine; Ranitidine hydrochloride; Stability indicating methods; Colorimetric methods

INTRODUCTION

Cimetidine (I), ranitidine hydrochloride (II) famotidine (III), are histamine H_2-receptor antagonists which inhibit gastric acid secretions, so these drugs are efficient in the treatment and prevention of recurrent duodenal ulcer.[2,3]

Several methods were reported for the determination and identification of cimetidine (I) including: titrimetry,[4,5] spectrophotometry,[6,7] fluorimetry,[8] colorimetry,[9] potentiometry,[10] capillary electrophoriesis,[11,12] voltammetry,[13] NMR,[14,15] infra red spectroscopy,[16] polarography,[17] TLC[18] and HPLC,[19–21] ranitidine hydrochloride (III) was determined by spectrophotometry,[22–24] colorimetry,[25,26] infra red spectroscopy,[27] flow injection analysis,[28,29] voltammetry,[30,31] potentio-

metry,[32] polarography,[33] capillary electrophoresis,[34,35] TLC[36] and HPLC,[37–40] for famotidine(III) several methods were applied including: spectrophotometry,[41–43] fluorimetry,[44] flow injection analysis,[45,46] capillary electrophoresis,[47] polarography,[48] voltammetery,[49] potentiometry,[50] TLC,[51–53] and HPLC.[54,55]

These three drugs are sulfur containing compounds, they can react with sodium nitroprusside in alkaline medium to produce color products which can be determined spectrophotometrically.[56,57] This method was reported for the determination of famotidine[56] but it has not reported for the determination of cimetidine and ranitidine hydrochloride.

In this work we try to develop sensitive spectrophotometric method. Sodium nitroprusside was used as a color reagent by applying ^{1}D for the determination of drug (I) and (II) using and ^{0}D for the determination of drug (III). The method is considered as stability indicating one, as the three drugs can be determined in the presence of their oxidative degradates.

Also two simple and sensitive spectrophotometric methods were developed for quantitative determination of (III) by using MBTH and a complex formation reaction with cobalt II.

EXPERIMENTAL

Apparatus

1. SHIMADZU 1601 PC UV vis. Spectrophotometer, using quartz cell ($1 \times 1 \times 3$ cm) slit width 2 nm.
2. Digital pH meter Pw 9409 Pye Unicam.

Reagents

All chemicals used were of analytical reagent grade and were used without further purification, the solvents were of spectroscopic grade.

1. Sodium nitroprusside (BDH) 2% w/v freshly prepared in distilled water.
2. Hydrochloric acid (E. Merck), 0.1 and 1 M aqueous solutions.
3. Sodium hydroxide (BDH), 1 M aqueous solution.
4. Ferric chloride (BDH), 4% w/v freshly prepared in 0.1 M HCl.
5. MBTH (Sigma), 0.35% w/v freshly prepared in 0.1 M HCl.
6. Cobalt chloride (BDH), 0.1% w/v prepared in distilled water.
7. Glacial acetic acid (E. Merck), 1 M aqueous solution.
8. Hydrogen peroxide solution 30% w/v (Adwic).

9. Ethyl acetate, iso-propanol, methanol, ammonia (E. Merck).
10. Silica gel 60 GF_{254} TLC plates (E. Merck).

Materials

Reference Samples

Cimetidine, famotidine and Ranitidine hydrochloride were kindly supplied by El-Arabia, Memphis and El-Nasr pharmaceutical companies, Cairo, Egypt, respectively. The purity of the samples was found to be 100.15 ± 0.762, 99.35 ± 0.652 and 99.63 ± 0.573, respectively according to B.P. methods 2000[1].

Market Samples

- Cimetidine tablets (El-Arabia) batch no. 115126. Each tablet was labelled to contain 200 mg of cimetidine.
- Tagamet tablets (Smith Kline Beecham) batch no 710010. Each tablet was labelled to contain 200 mg of cimetidine.
- Tagamet ampoules (Smith Kline Beecham) batch no. 007176. Each ampoule was labelled to contain 200 mg of cimetidine.
- Antodine tablets (Amoun) batch no. 480. Each tablet was labelled to contain 20 mg of famotidine.
- Famotin tablets (Memphis) batch no. 399326. Each tablet was labelled to contain 40 mg of famotidine.
- Gastrodomina tablets (Medical Union Pharmaceuticals) batch no. 990634. Each tablet was labelled to contain 40 mg of famotidine.
- Ranitac tablets (South Egypt Drug Industries Company) batch no. 100103. Each tablet was labelled to contain 40 mg of ranitidine hydrochloride.
- Zantac tablets (Glaxo Welcome) batch no. 90056A. Each tablet was labelled to contain 150 mg of ranitidine hydrochloride.
- Zantac ampoules (Glaxo Welcome) batch no. 80784A. Each ampoule was labelled to contain 150 mg of ranitidine hydrochloride.

Degraded Samples

Oxidative degradates were prepared as stock solutions of $10\,mg{\cdot}mL^{-1}$. One gram of each pure drug was accurately weighed and transferred into small conical flasks, dissolved in 10 mL of 0.1 N HCl for (I) and (III) and in

10 mL water for (II), 1 mL of 30% hydrogen peroxide solution was added to each drug. The solutions were heated in a boiling water bath for 3 h for (I) and (III) and 40 min for (II), then the solutions were quantitatively transferred into 100-mL volumetric flask and the volume was completed to the mark with water. The solutions were tested for complete degradation by TLC using ethyl acetate: isopropanol: 20% ammonia (9:5:4 v/v) for cimetidine and famotidine and ethyl acetate: methanol: 20% ammonia (10:2:2 v/v) for ranitidine hydrochloride as mobile phases.

Standard Solutions (Stock Standard Solutions)

Cimetidine

A stock standard solution of 0.5 mg·mL^{-1} was prepared by dissolving 50 mg of cimetidine in the least amount of 0.1 N HCl (0.5 mL) into 100-mL measuring flask, the volume was then completed with water.

Ranitidine Hydrochloride

A Stock standard solution of 1 mg·mL^{-1} was prepared by dissolving 100 mg of ranitidine hydrochloride and famotidine in 10 mL water in a 100-mL volumetric flask then the volume was completed with water.

Famotidine

For the first and the second methods; a 1 mg·mL^{-1} stock standard solution was prepared by dissolving 100 mg of famotidine in 1 mL 0.1 N HCl in a 100-mL volumetric flask, the volume was completed to the mark with distilled water, for the third method ; a 0.5 mg·mL^{-1} stock standard solution was prepared by dissolving 50 mg of famotidine in 0.5 mL 1 M acetic acid in a100-mL measuring flask the volume was then completed to the mark with distilled water.

Working Degraded Standard Solutions

The degradate working standard solution was prepared by transferring 5 mL of degraded cimetidine and 10 mL of degraded ranitidine hydrochloride and famotidine respectively in 100-mL volumetric flasks then the volume was completed with water.

PROCEDURE

Construction of Calibration Curves

For the First Method (Using Sodium Nitroprusside)

Different aliquots equivalent to (0.25–1.5 mg) of drug (I) and (0.5–5.0 mg) of both (II) and (III) were separately transferred form their stock standard solutions into a series of 10-mL volumetric flasks, 1 mL of 1 N sodium hydroxide solution was added followed by 2 mL of sodium nitroprusside solution (2%). Then 2 mL of 1 N HCl was added after 15 min for (I) and 5 min for both (II) and (III) minutes to stop the reaction, the volume was completed with distilled water. The absorbance values using the zero-order spectrum ^{0}D at 500 nm was measured for the determination of drug (III) and first derivative amplitude using ^{1}D at 523 and 510 nm for the determination of both (I) and (II) drugs were recorded against a blank prepared similarly. Plot the absorbance A in case of ^{0}D and the peak amplitude H in case of ^{1}D against the corresponding concentration of each drug to obtain linearities. Compute the regression equations for each drug.

For the Second Method (Using MBTH)

Different aliquot portions from drug (III) stock standard solution equivalent to (0.5–3.0 mg) were transferred into a series of 25-mL volumetric flasks. 4 mL of (MBTH) solution (0.35% w/v) was added followed by 4 mL of Ferric Chloride solution (4%w/v), the solutions were kept for 60 min at room temperature then the volume was completed with distilled water. The absorbance was measured after 15 min at 536 and 620 nm against a blank prepared similarly. Linear calibration curve was obtained by plotting the absorbance against the corresponding concentration of the drug.

For the Third Method (Using Cobalt II)

Different aliquot portions from drug (III) standard stock solution equivalent to (0.25–1.50 mg) were transferred into a series of 25-mL volumetric flasks, 2 mL of borate buffer (Ph = 9.6) was added followed by 3 mL of Cobalt Chloride solution (0.1%w/v) the solutions were kept for 15 min at room temperature then the volume was completed with distilled water. The absorbance of the formed complex at 319 nm was measured against a blank prepared similarly, and plotted against the drug concentration producing a linear correlation.

Assay of Laboratory Prepared Samples

Prepare mixtures containing from 10–90% of degradate with the intact drug. Proceed as under construction of calibration curves for the first method. The concentrations were calculated from the corresponding regression equations. Prepare unknown samples of drug III and proceed as under construction of calibration curve for the second and third methods then calculate the concentrations from the corresponding regression equation.

Assay of Dosage Forms

For tablets, twenty tablets of each drug were accurately weighed and finely powdered an amount equivalent to 50 mg of drug (I), 100 mg of (II) and for (III), 100 mg for the first and the second methods and 50 mg for the third method. These powders were separately transferred into 100-mL volumetric flasks shaken with the same solvents as mentioned under stock standard solutions, completed to volume and filtered.

For injections, ten ampoules of each drug were mixed together, a volume equivalent to 50 mg and 100 mg of drug (I) and (II), respectively was separately transferred into 100-mL volumetric flask then the volume was completed with distilled water. Proceed as mentioned under construction of calibration curve for the three previously mentioned methods, calculate the concentration of each drug in its pharmaceutical dosage forms from the corresponding regression equation.

The standard addition technique was applied by mixing 5 different concentrations of the raw material with the powdered tablets then proceed as under the assay of tablets. The % recoveries were calculated using the corresponding regression equation.

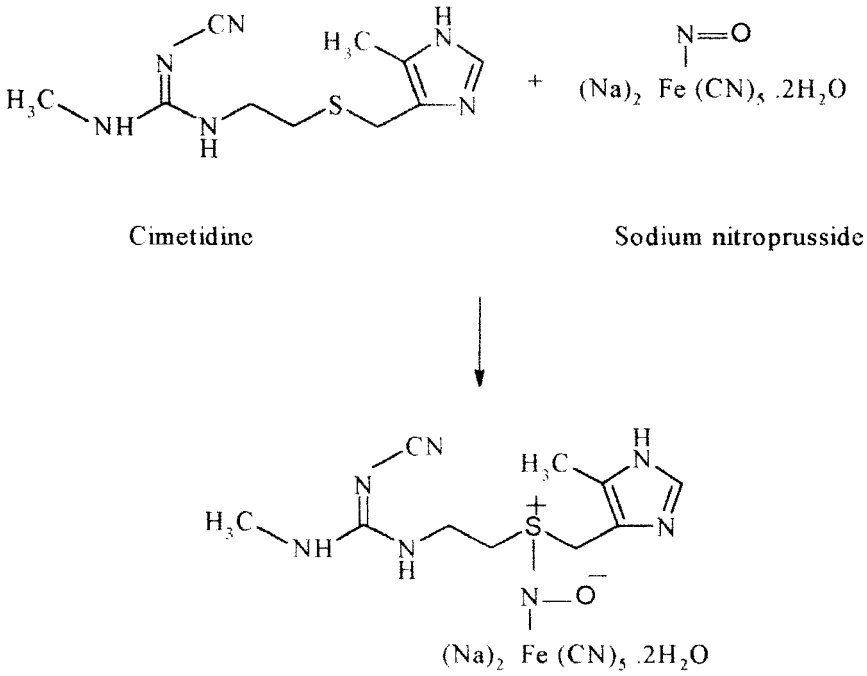
RESULTS AND DISCUSSION

Cimetidine (I), famotidine (II) and ranitidine hydrochloric (III) are structurally related H2 receptor antagonists used for the treatment of duodenal ulcer, their structure activity relationship shows that their S-oxide are inactive as H_2 receptor antagonist.[58]

As these drugs contain sulfur atom which make them liable to form S-oxide derivatives on exposure to either atmospheric oxidation or under storage conditions.[57] We enhance the formation of these derivatives by treating them with 30% hydrogen peroxide solution, the (S-oxides) derivatives are inactive, so it is very important to develop a method for the determination of these pure drugs and their dosage forms in presence of their oxidative degradates.

In the first method, sodium nitroprusside is used, it is a valuable reagent for the detection and determination of sulfur containing compounds, its reactivity is based on the reaction of the positive nitrosyl group with neucleophillic species (mostly in alkaline medium),[56,57] so the nitrosyl derivative of the three drugs were formed having a red color but in case of the oxidative degradates the sulfur atom no longer being a neucleophile and so no addition product will be formed. Therefore we can apply this method as a stability indicating for the determination of these drugs, the stiochiometry of the reaction was studied and the molar ratio was found to be (1:1) for all drugs, the optimum reaction conditions were carefully established.

The suggested mechanism for the Reaction 1 is as follows:



Reaction 1.

Famotidine can be directly determined without any interference from its oxidative degradate using the zero order spectra at λ 500 nm, see Fig. 1. On the other hand, Fig. 2 and 3 show that there is a marked overlapping in the ^{0}D spectra of the reaction products of the drugs (I) and (II) and their

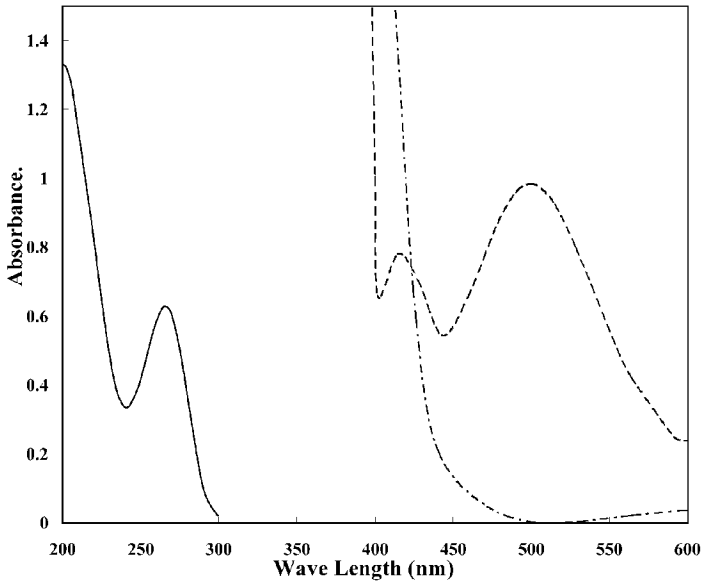


Figure 1. Zero-order absorption spectra of: famotidine, 20.00 $\mu g \cdot ml^{-1}$ (——); famotidine–nitroprusside, 500.00 $\mu g \cdot ml^{-1}$ (- - - -); degraded famotidine–nitroprusside, 500.00 $\mu g \cdot ml^{-1}$ (—·—·—).

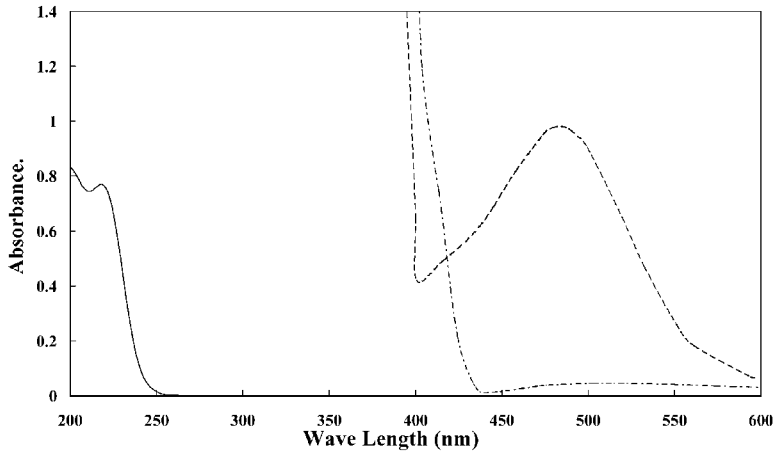


Figure 2. Zero-order absorption spectra of: cimetidine, 10.00 $\mu g \cdot ml^{-1}$ (——); cimetidine–nitroprusside, 150.00 $\mu g \cdot ml^{-1}$ (- - - -); degraded dimetidine–nitroprusside, 150.00 $\mu g \cdot ml^{-1}$ (—·—·—).

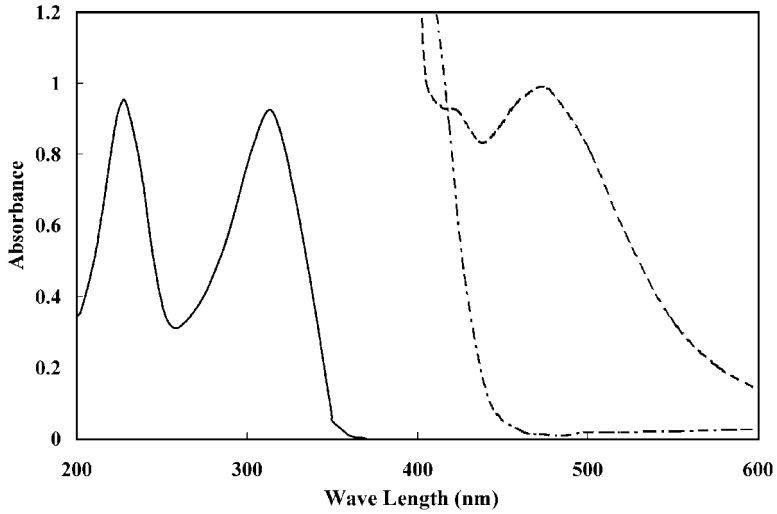


Figure 3. Zero-order absorption spectra of: ranitidine hydrochloride, 20.00 μg·ml^{-1} (——); ranitidine·HCl–nitroprusside, 500.00 μg·ml^{-1} (- - - -); degraded ranitidine HCl–nitroprusside, 500.00 μg·ml^{-1} (—·—·—).

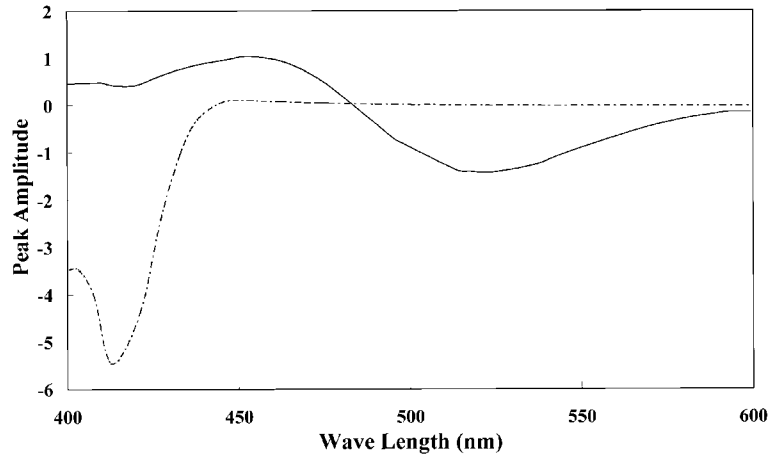


Figure 4. First derivative spectra (^{1}D) of nitroprusside reaction products with cimetidine (——) and its degradate (—·—·—) [150.00 μg·ml^{-1} of each].

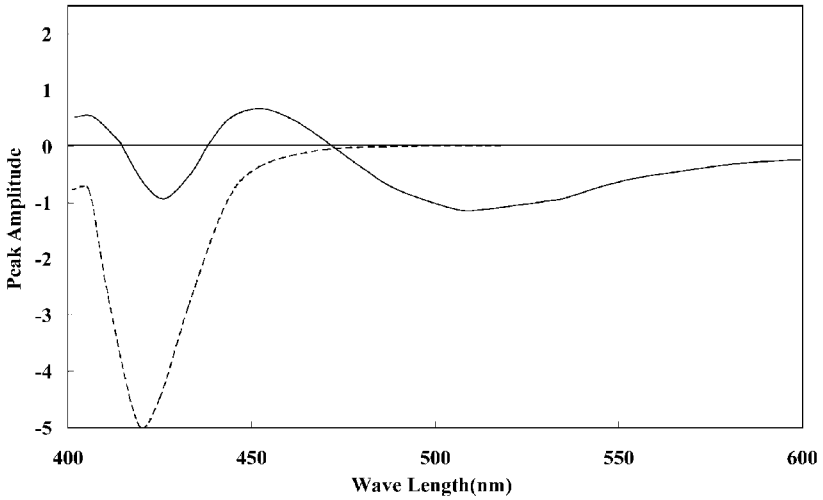


Figure 5. First derivative spectra (^{1}D) of nitroprusside reaction products with ranitidine hydrochloride (——) and its degradate (- - - -) [500.00 μg·ml^{-1} of each].

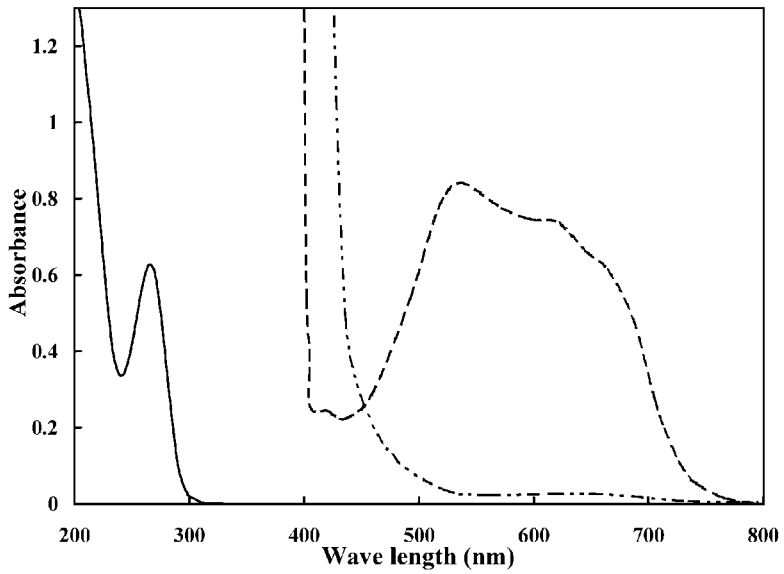


Figure 6. Zero-order absorption spectra of: famotidine, 20.00 μg·ml^{-1} (——); blank reagent (—·—·—); famotidine–MBTH, 100.00 μg·ml^{-1} (- - - -).

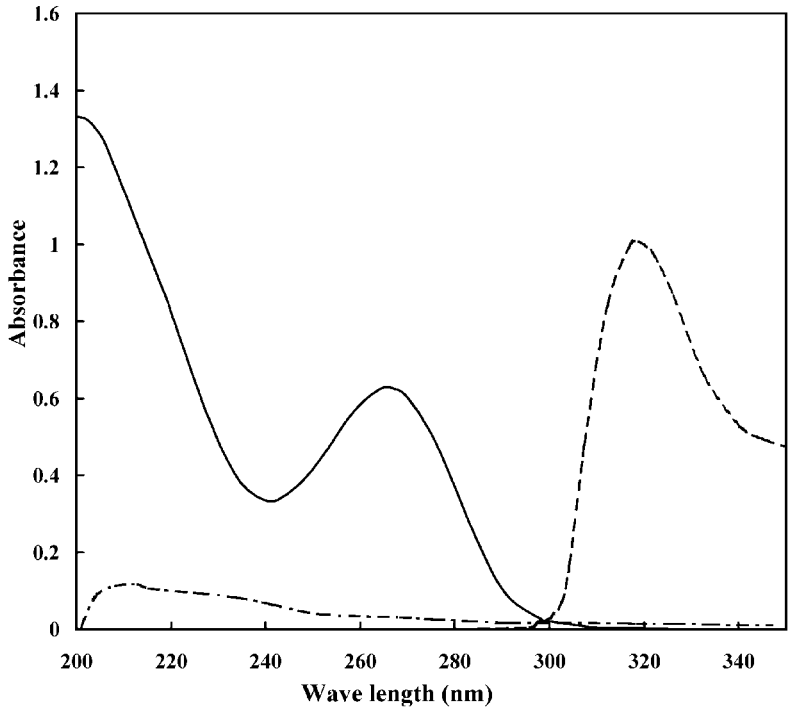
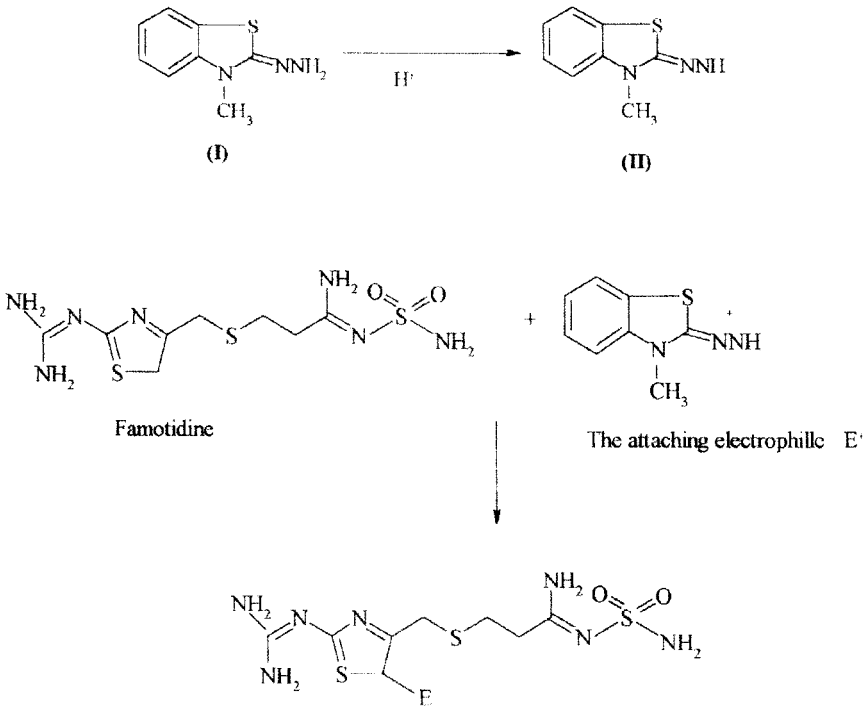


Figure 7. Zero-order absorption spectra of: famotidine, 20.00 μg·ml^{-1} (——); famotidine–cobalt (II) complex, 60.00 μg·ml^{-1} (- - - -); blank reagent (—·—·—).

oxidative degradates which can be overcomed by using ^{1}D curves at $\Delta\lambda = 4$ nm. Figs. 4 and 5. Beer's law was obeyed in the concentration range of 25–150 μg mL^{-1} for (I) and 50–500 μg mL^{-1} for (II) and (III) with mean percentage recoveries of 100.27 ± 0.697, 99.79 ± 0.465 and 99.15 ± 0.687 for the three drugs, respectively.

In the second method: 3-Methyl-2- benzothiazolinone hydrazone (MBTH) was used as color reagent, it was reported for the determination of ranitidine hydrochloride.[59] It reacts with drug (III) via oxidative coupling,[60] MBTH losses two electrons and one proton on oxidation with oxidizing agent (e.g., ferric chloride) forming electrophillic intermediate, which is the active coupling species.[61] The reagent would be expected to attach the carbon atom with maximum electron density as in drug (III) to form bluish violet colored product as shown in the following Sch. 1:

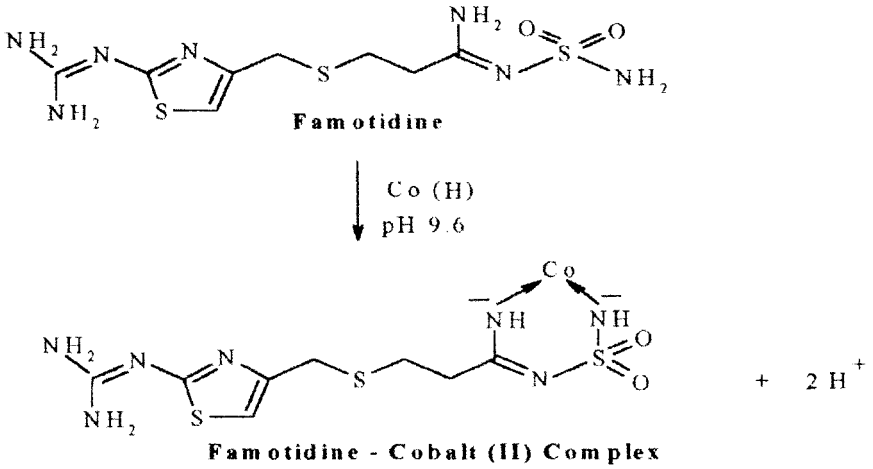


Scheme 1.

The optimum conditions of the reaction, effect of volume of MBTH and ferric chloride and the effect of time were studied. The molar ratio was determined and found to be (1:1). Drug III-MBTH reaction product has two absorption maxima at 536 and 620 nm Fig. 6, both were used for the determination of drug (III) Beer's law was obeyed in the concentration range of 20–120 $\mu g\,mL^{-1}$ with mean percentage recoveries of 99.73 ± 1.048 and 99.94 ± 0.887 at 536 and 620 nm, respectively.

The third method is a spectrophotometric method, it is used for the determination of drug (III) via its complex formation reaction with cobalt II ions to produce a colorless complex having λ^{max} at 319 nm Fig. 7. Various parameters were studied such as the effect of cobalt II concentration, the effect of pH, the effect of time and the molar ratio was determined and found to be (1:1), the calculated stability constant logarithm was 5.49. Beer's law was obeyed in the concentration range of 10–60 $\mu g.\,mL^{-1}$ with mean percentage recovery of 99.84 ± 0.858.

The suggested Reaction 2 product as follows:



Reaction 2.

Table 1. Colorimetric Determination of Cimetidine, Ranitidine Hydrochloride, and Famotidine with Their Corresponding Oxidative Degradates Using Sodium Nitroprusside in Laboratory Prepared Mixtures

	Percentage Recovery* of Intact Drug		
% of Degradate	Cimetidine (Using ^1D at $\lambda = 523$ nm)	Ranitidine Hydrochloride (Using ^1D at $\lambda = 510$ nm)	Famotidine (Using ^0D at $\lambda = 500$ nm)
10	98.97	100.46	100.25
20	100.61	99.79	99.68
30	98.99	99.32	100.32
40	99.60	98.98	100.65
50	98.67	100.65	101.01
60	100.40	101.01	101.35
70	101.00	99.89	98.56
80	100.68	100.35	99.65
90	99.15	100.98	98.98
Mean ± RSD%	99.78 ± 0.890	100.16 ± 0.712	100.05 + 0.917

* The average of three different determinations.

Table 2. Application of Standard Addition Technique for the Determination of Cimetidine, Ranitidine Hydrochloride, and Famotidine by the Proposed Methods

Cimetidine		Ranitidine Hydrochloride		Famotidine				
	Recovery %*		Recovery %*		Recovery %*			
						Second Method		
Preparation	First Method	Preparation	First Method	Perparation	First Method	At 536 nm	At 620 nm	Third Method
Tagamet tablets 200 mg tablet^{-1} B.N. 710010	100.15 ± 0.691	Zantac tablets 150 mg tablet^{-1} B.N. 990056A	100.27 ± 0.657	Antodine tablets 40 mg tablet^{-1} B.N. 480	100.32 ± 0.369	100.32 ± 0.504	100.14 ± 0.764	100.29 ± 1.006
Tagamet ampoules 200 mg ampoule^{-1} B.N. 007176	99.81 ± 0.370	Ranitac tablets 300 mg tablet^{-1} B.N. 100103	99.93 ± 0.821	Famotin tablets 40 mg tablet^{-1} B.N. 399326	99.86 ± 0.598	100.02 ± 0.592	100.64 ± 0.715	100.36 ± 0.726
Cimetidine tablets 200 mg tablet^{-1} B.N. 115126	100.14 ± 0.588	Zantac ampoules 150 mg ampoule^{-1} B.N. 80784A	100.19 ± 0.458	Gastrodomina tablets 40 mg tablet^{-1} B.N. 990634	99.63 ± 0.852	100.30 ± 0.936	99.69 ± 0.754	100.10 ± 523

* The recoveries obtained by the proposed methods are the average of 5 experiments.

Table 3. Results of Assay Validation Obtained by Applying the Proposed Colorimetric Method Using Sodium Nitroprusside

Parameters	Cimetidine	Ranitidine Hydrochloride	Famotidine
Range ($\mu g \cdot mL^{-1}$)	25.00–150.00	50.00–500.00	50.00–500.00
LOD ($\mu g \cdot mL^{-1}$)	2.832	8.57	11.56
LOQ ($\mu g \cdot mL^{-1}$)	20.60	45.65	43.56
Slope	0.009	0.0022	0.0019
Intercept	0.0719	0.0339	0.0207
Correlation Coeff. (r)	0.9999	0.9999	0.9999
Mean ± RSD%	100.27 ± 0.697	99.79 ± 0.465	99.15 ± 0.687
RSD%*,[a]	0.781–1.531	0.431–0.567	0.871–0.976
RSD%*,[b]	0.531–0.671	0.432–0.510	0.671–0.732

*,[a] The interday (n = 5) and *,[b] the intraday (n = 7) relative standard deviations of samples concentration (50 and 125 $\mu g \cdot mL^{-1}$) for Cimetidine and (100.00 and 400.00 $\mu g \cdot mL^{-1}$) for ranitidine hydrochloride and famotidine, respectively.

Table 4. Results of Assay Validation Obtained by Applying the Second (Using MBTH) and the Third (Using Cobalt II) Methods

	The Second Method		
Parameter	At 536 nm	At 620 nm	The Third Method
Range ($\mu g \cdot mL^{-1}$)	20.00–120.00	20.00–120.00	10.00–60.00
LOD ($\mu g \cdot mL^{-1}$)	3.14	3.52	2.224
LOQ ($\mu g \cdot mL^{-1}$)	12.362	12.670	8.046
Slope	0.0084	0.0075	0.0174
Intercept	−0.0073	−0.0105	0.0193
Correlation Coeff. (r)	0.9998	0.9999	0.9999
Mean ± RSD%	99.73 ± 1.048	99.94 ± 0.887	99.84 ± 0.858
RSD%*,[a]	1.213–2.05	0.895–0.967	0.679–0.789
RSD%*,[b]	0.987–1.031	0.731–0.898	0.573–0.689

*,[a] The interday (n = 5) and *,[b] the intraday (n = 7) relative standard deviations of samples concentration (40.00 and 100.00 $\mu g \cdot mL^{-1}$) of famotidine for the second method and (20.00 and 50.00 $\mu g \cdot mL^{-1}$) of famotidine for the third method.

Table 5. Statistical Comparison Between the Results of the Proposed Methods and the Official B.P. 2000 Method on the Analysis of Cimetidine, Ranitidine Hydrochloride, and Famotidine

	Cimetidine		Ranitidine Hydrochloride		Famotidine				
						Second Method			
Values	First Method	Official** Method	First Method	Official** Method	First Method	At 536 nm	At 620 nm	Third Method	Official** Method
Mean	100.27	100.15	99.79	99.63	99.15	99.73	99.94	99.84	99.35
S.D.	0.699	0.762	0.463	0.573	0.681	1.045	0.888	0.857	0.652
R.S.D.%	0.697	0.761	0.464	0.575	0.687	1.048	0.888	0.858	0.656
Variance	0.489	0.581	0.214	0.328	0.464	1.092	0.788	0.734	0.425
n	6	6	6	6	6	6	6	6	6
F (5.05)*	1.188		1.533		1.092	2.596	1.166	1.727	
Student's (2.228)*	0.243		0.518		0.425	0.691	1.854	0.977	

* The values between parenthesis are the corresponding theoretical values of t and F at ($p = 0.05$).
** The official methods are the British pharmacopoeial methods 2000.

The concentration of each drug was calculated using the following regression equations.

For the first method (using sodium nitroprusside):

$H = 0.009X + 0.0719 \quad r = 0.9999 \quad$ forcimetidine(I) $\quad {}^{1}D$

$H = 0.0022X + 0.0339 \quad r = 0.9999 \quad$ forranitidinehydrochloride(II) $\quad {}^{1}D$

$A = 0.0019X + 0.0207 \quad r = 0.9999 \quad$ forfamotidine(III) $\quad {}^{0}D$

For the second method (using MBTH):

$A = 0.0084X - 0.0073 \quad r = 0.9998 \quad$ at 536nm

$A = 0.0075X - 0.0105 \quad r = 0.9999 \quad$ at 620nm

For the third method (using Co II):

$A = 0.0174X + 0.0193 \quad r = 0.9999$

The first method applied to the analysis of the drugs in presence of their oxidative degradates and all the described methods were used for the determination of the studied drugs in commercial tablets and injections, the validity of these methods was assessed by applying the standard addition technique and assay validation. The results obtained are presented in Tables 1–4. The obtained results were statistically compared with those obtained by the official methods, Table 5 shows that the calculated t and F values are less than the theoretical ones confirming the accuracy and precision at the 95% confidence limit. From the previous results we see that the suggested methods show high sensitivity, accuracy and reproducibility in addition to the specificity of sodium nitroprusside method as it can be used as stability indicating method for the three drugs in presence of their corresponding oxidative degradates. So they can be applied in routine and quality control laboratories.

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