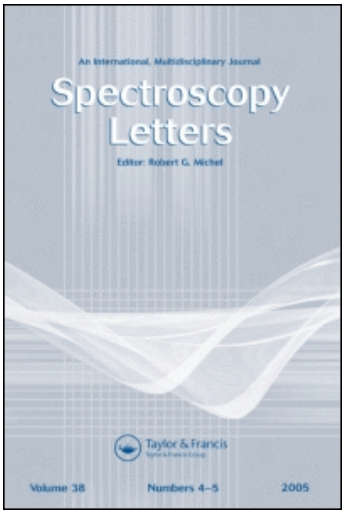

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STABILITY INDICATING METHOD FOR THE DETERMINATION OF NIZATIDINE USING 3-METHYL-2-BENZOTHIAZOLINONE HYDRAZONE

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STABILITY INDICATING METHOD FOR THE DETERMINATION OF NIZATIDINE USING 3-METHYL-2-BENZOTHIAZOLINONE HYDRAZONE

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ABSTRACT

A sensitive stability indicating method for the determination of nizatidine in the presence of its degradation products is developed. The proposed method is based on measuring the peak heights of the first derivative spectra at 680 nm of the blue reaction product developed from the reaction of nizatidine with 3-methyl-2-benzothiazolinone hydrazone (MBTH) in the presence of ferric chloride. The concentration of MBTH, and type of oxidising agent and its concentration were studied over time. The suggested procedure is simple, rapid and readily adaptable for the determination of pure nizatidine in bulk powder. Laboratory prepared mixtures and pharmaceutical preparations in the range of 1.6–8 $\mu g \cdot ml^{-1}$ of reaction mixture can be analysed. The results obtained were compared statistically with those obtained by applying the official USP XXIII (1995) method. Furthermore, the validity of the results was assessed by applying the standard addition technique.

Key Words: Nizatidine; Spectrophotometry; Stability indicating method; Pharmaceuticals.

INTRODUCTION

The histamine H_2 receptor antagonists are among the most effective antisecretory drugs available for management of acid peptic diseases. This class of drugs was developed with the aim of producing agents for the treatment of peptic ulcer (1).

Nizatidine is a specific, potent H_2 receptor antagonist. Unlike cimetidine, which contains an imidazole ring structure, or ranitidine, which contains a furan ring structure, nizatidine has a thiazolyl ring structure. This structure is more potent than cimetidine for inhibition of gastric acid secretion induced by various stimuli. However nizatidine lacks cimetidine's anti-androgenic and hepatic microsomal enzyme inhibiting effects (2,3). Nizatidine has been used in the treatment of duodenal ulceration (4).

Chemically, nizatidine is N-[2[[[2-[(dimethylamino)methyl]-4-thiazolyl] methyl]thio]ethyl]-N-methyl-2-nitro-1,1-ethenediamine. Few methods have been reported for the analysis of nizatidine, these include; spectrophotometric (5), coulometric (6) and HPLC (7–9) methods. It has been proven that MBTH hydrochloride is a sensitive chromogenic reagent for the spectrophotometric determination of some nitrogen containing drugs including those with the heterocyclic ring (10–13), sulpha drugs (14) and some phenolic drugs (15,16).

The objective of this work was the development of a simple and rapid spectrophotometric stability indicating method for the determination of nizatidine. The proposed procedure is based on the formation of a stable blue colored oxidative-coupling product using MBTH in presence of ferric chloride. The proposed method is devoted to the application of the first derivative technique of the colored product at 680 nm.

EXPERIMENTAL

Samples

Authentic samples of nizatidine Lot 541 GH1, nizatidine amide Lot 9424EW 163, and nizatidine sulfoxide Lot A558BM1212, were supplied by Eli-Lilly & Co. Indianapolis U.S.A. Axid 150 capsules manufactured by Eli-Lilly & Co., batch Nos. 7CL81B, 7AT50F, 6NY76B, 5AG66A, 5EH50B and 5CR21C, with a claim to contain 150 mg of nizatidine per capsule. Axid 300 capsules manufactured by Eli-Lilly & Co., batch No. 6LF20E, 6EH30B, 7NY83B and 7AT60F, with a claim to contain 300 mg of nizatidine per capsule were purchased.

Reagents and Solutions

3-Methyl-2-Benzothiazolinone Hydrazone (MBTH) Hydrochloride (Sigma Chemical Co. U.S.A.) solution was freshly prepared as (0.35% w/v) solution in Hydrochloric acid (0.1 M). Ferric chloride (E. Merck, W. Germany) was prepared as (1% w/v) solution in Hydrochloric acid (0.1 M). Hydrochloric acid (E. Merck, W. Germany) was prepared as (0.1 M) solution.

Stock Solutions

($80\ \mu g \cdot ml^{-1}$) of nizatidine, nizatidine sulfoxide and nizatidine amide were prepared in distilled water.

Laboratory Prepared Mixtures

These were prepared by transferring accurately equal aliquot portions (2–10 ml) of nizatidine amide and nizatidine sulfoxide from their stock solutions into a series of 100 ml volumetric flasks. The volume was completed with complementary volumes of nizatidine stock solution.

Apparatus

A Beckman Instruments Du-7 spectrophotometer was used for all absorbance measurements.

Procedures

Linearity

Accurate measured aliquots, equivalent to 80–400 μg. of nizatidine from its stock solution ($80\ \mu g \cdot ml^{-1}$), were transferred into a series of 50 ml volumetric flasks. Complementary volumes of distilled water were added to adjust the volume to 5 ml. Then 2 ml of MBTH solution (0.35 % w/v) and 5 ml of ferric chloride solution (1% w/v) were added. The flasks were kept at room temperature for one hour then completed to volume with distilled water. The zero–order absorption at 613 nm, 651 nm (Fig. 1) and the first derivative spectra at 680 nm (Fig. 2) were recorded against an appropriate blank similarly prepared using 5 ml distilled water instead of nizatidine.

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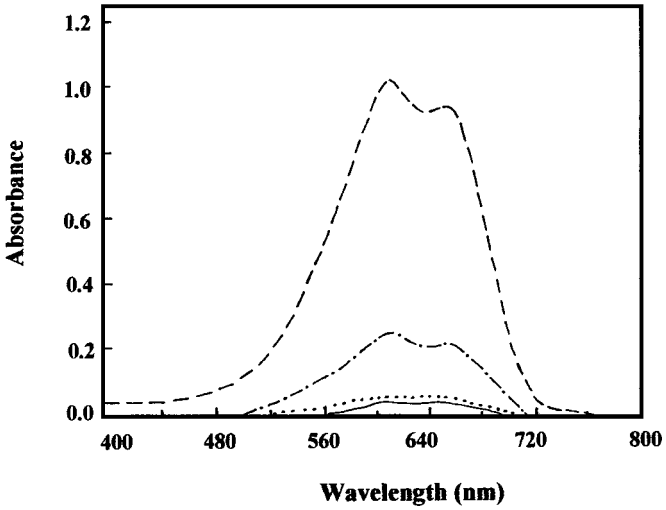

Figure 1. Zero-order absorption spectra of reaction products of MBTH with nizatidine {1.6 μg · ml^{-1}} (-·-), nizatidine {8 μg · ml^{-1}} (---), nizatidine amide {0.32 μg · ml^{-1}} (——), nizatidine sulfoxide {0.32 μg · ml^{-1}} (· · · · ·).

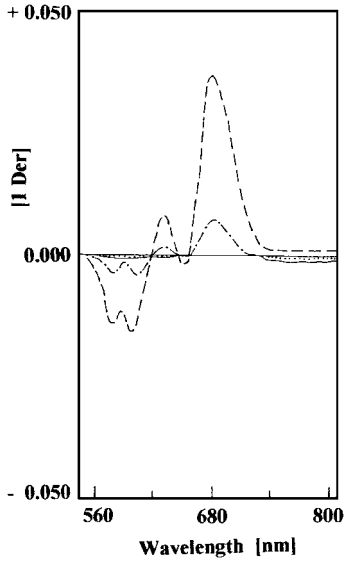

Figure 2. First derivative spectra of reaction products of MBTH with nizatidine {1.6 μg · ml^{-1}} (-·-), nizatidine {8 μg · ml^{-1}} (---), nizatidine amide {0.32 μg · ml^{-1}} (——), nizatidine sulfoxide {0.32 μg · ml^{-1}} (· · · · ·).

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Table 1. Comparison Between the Results Obtained by Applying the Proposed Colorimetric Method and the Official USP XXIII 1995 Method for the Analysis of Nizatidine in Its Laboratory Prepared Mixtures

	Degradation Products (%) Added		Found (%) of Pure Nizatidine			
			Colorimetric Method			
Sample No.	Nizatidine Amide (%)	Nizatidine Sulfoxide (%)	Zero-Order Absorption at 613 nm	Zero-Order Absorption at 651 nm	First Derivative at 680 nm	Official Method
1	2.0	2.0	100.98	101.02	99.97	100.02
2	4.0	4.0	102.14	102.35	99.88	99.87
3	6.0	6.0	107.64	108.01	100.00	100.02
4	8.0	8.0	117.40	118.09	100.02	99.92
5	10.0	10.0	130.94	132.36	99.96	100.06
	$\bar{X} \pm$ S.D.				99.97 ± 0.05	99.98 ± 0.08

$\bar{X}$: Mean.
S.D. : Standard Deviation.

Reproducibility in the Presence of the Degradation Products

Accurately measured 2.0 ml of each of the laboratory prepared mixtures containing different ratios of nizatidine and its degradation products were transferred into a series of 100 ml volumetric flasks. The volume was adjusted to 5 ml with distilled water, then proceeded as described under linearity. The concentration of nizatidine in the prepared mixtures can be determined by reference to the corresponding regression equations. The results obtained were compared with those obtained by applying the official USP XXIII (1995) method as shown in Table 1.

Application of the Proposed Procedure to the Analysis of Pharmaceutical Preparations

The content of not less than ten accurately weighed capsules were removed as completely as possible and mixed. The net weight of the capsule contents was determined. An accurately weighed portion equivalent to 320 mg of nizatidine was transferred to a 100 ml beaker. 80 ml of distilled water was added and the solution was stirred with magnetic stirrer for 30 minutes and filtered through filter paper into a 100 ml volumetric flask. The volume was completed

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Table 2. Comparison of the Results Obtained by Applying the Proposed Colorimetric Method and Those of the Official USP XXIII 1995 Method for the Determination of Nizatidine in Its Pharmaceutical Preparations

	Colorimetric Method			
	Zero-Order Absorption		First Derivative	
Preparation	at 613 nm $\bar{X} \pm$ S.D.	at 651 nm $\bar{X} \pm$ S.D.	at 680 nm $\bar{X} \pm$ S.D.	Official Method
Axid 150 Cap. B.N. 7CL81B	99.21 ± 0.22	99.26 ± 0.28	99.18 ± 0.32	99.10 ± 0.26
Axid 150 Cap. B.N. 6NY76B	97.45 ± 0.38	97.56 ± 0.33	97.47 ± 0.41	97.54 ± 0.31
Axid 150 Cap. B.N. 5AG66A	95.99 ± 0.49	95.97 ± 0.52	96.01 ± 0.44	96.09 ± 0.65
Axid 150 Cap. B.N. 5EH50B	100.01 ± 0.22	99.99 ± 0.25	100.01 ± 0.17	99.98 ± 0.12
Axid 150 Cap. B.N. 7AT50F	99.22 ± 0.29	99.40 ± 0.21	99.29 ± 0.24	99.12 ± 0.19
Axid 150 Cap. B.N. 5CR21C	99.60 ± 0.27	99.72 ± 0.31	99.59 ± 0.28	99.65 ± 0.24
Axid 300 Cap. B.N. 6LF20E	100.03 ± 0.38	100.01 ± 0.41	99.99 ± 0.43	100.06 ± 0.39
Axid 300 Cap. B.N. 7AT60F	99.74 ± 0.34	99.81 ± 0.31	99.89 ± 0.26	99.89 ± 0.29
Axid 300 Cap. B.N. 7EH30B	99.21 ± 0.25	99.30 ± 0.19	99.18 ± 0.23	99.11 ± 0.17
Axid 300 Cap. B.N. 7NY83B	99.76 ± 0.41	99.69 ± 0.38	99.72 ± 0.36	99.82 ± 0.32

$\bar{X}$: Mean of five different experiments.
S.D. : Standard Deviation.

with the washing. An appropriate dilution was done to prepare the working solution ($80\ \mu g \cdot m^{-1}$). Different aliquot portions (1–5 ml) from the working solution were transferred to a series of 50 ml volumetric flasks and details described under linearity were used. The concentration of nizatidine can be determined by reference to the corresponding regression equations. The results obtained were compared with those obtained by applying the official USP XXIII (1995) method as shown in Table 2.

Determination of the Ratio of Nizatidine-MBTH by Continuous Variation Method

Accurately measured 1, 2, ... and 9 ml of 4.5×10^{-4} M nizatidine solution were added to 9, 8, ... and 1 ml of 4.5×10^{-4} M MBTH into a series of 50 ml volumetric flasks. Then 5 ml of ferric chloride solution (1% w/v) was added and the solutions were kept for one hour then completed to volume with distilled water. The absorbance of each flask was measured at 613 nm and 651 nm against an appropriate blank prepared similarly using 5 ml distilled water instead of the nizatidine. The results obtained were represented graphically in Figure 3.

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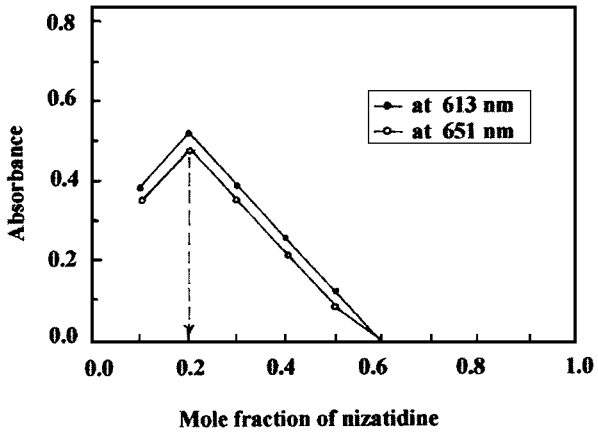

Figure 3. Determination of the stoichiometry of the reaction of nizatidine and MBTH by the continuous variation method using 4.5×10^{-4} M solutions.

Determination of the Ratio of Nizatidine Amide-MBTH by Continuous Variation Method

The procedure described in the section immediately preceding this was followed using 5×10^{-4} M solution (rather than 4.5×10^{-4} M) of both nizatidine amide and MBTH. The absorbance of each flask was measured at 622 nm and 660 nm. The results obtained were represented graphically in Figures 4 and 5.

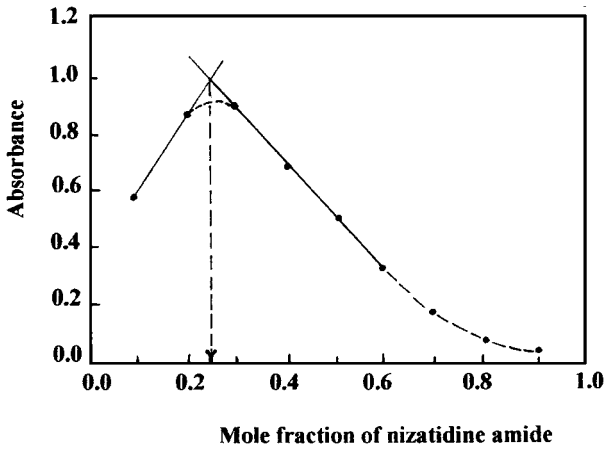

Figure 4. Determination of the stoichiometry of the reaction of nizatidine amide and MBTH at 622 nm by the continuous variation method using 5×10^{-4} M solutions.

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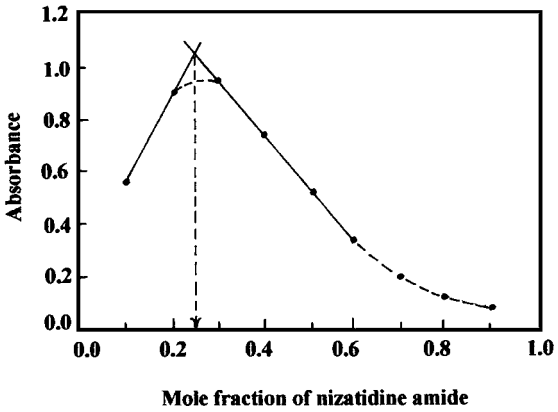


Figure 5. Determination of the stoichiometry of the reaction of nizatidine amide and MBTH at 660 nm by the continuous variation method using 5×10^{-4} M solutions.

RESULTS AND DISCUSSION

The Proposed Reaction

The reaction of MBTH with heterocyclic nitrogenous compounds in the presence of an oxidant (17), proceeds via oxidative-coupling. MBTH (I) loses two electrons and one proton on oxidation with the oxidising agent (i.e., ferric chloride), forming the electrophilic intermediate (II), which is the active coupling species (18).

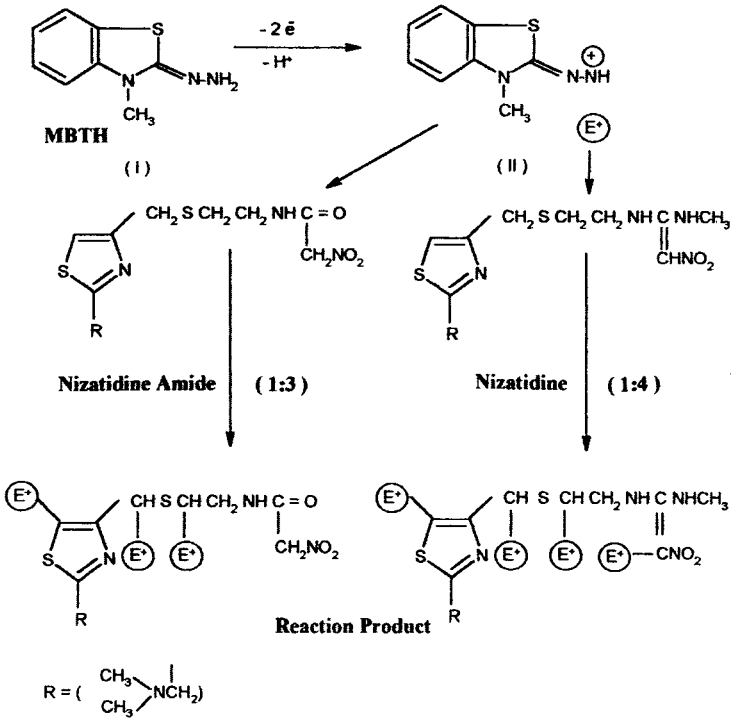
The reagent would be expected to attack carbon atoms with a maximum electron density such as in carbazol and phenothiazine; it attacks the position para to the nitrogen of the ring while, in indole compounds the 3-position is most active. Position 5, i.e., para to the ring nitrogen is the most active when positions 2 and 3 are occupied.

The suggested assumption for the reaction of nizatidine and nizatidine amide with MBTH is shown in Scheme 1.

This Assumption Was Assessed by:

Five membered heterocycles with oxygen, sulfur or nitrogen undergo electrophilic coupling predominantely at the 2-position (18,19). Reactions of MBTH with amines were found to be similar to that of diazonium salts (19–21).

The N-coupling product is kinetically favored while the C-coupling product is thermodynamically favored (20,22). Since the proposed procedure using MBTH



Scheme 1.

was carried out in strong acid medium (pH = 2) so, the reaction is a coupling reaction (23–26). Hydrogen atoms on carbon atoms that are adjacent to an alkylthio group are acidic, so it can be substituted by an electrophile (19).

Investigation of the continuous variation method showed that nizatidine interacts with MBTH in the ratio 1:4, while nizatidine amide interacts with MBTH in the ratio 1: 3. This may be due to the $-C{=}CH\ NO_2$ group of nizatidine converting into $=C{-}CH_2\ NO_2$ group, while the three other sites of attacks are similar. Investigation of the continuous variation method of ranitidine and MBTH showed that ranitidine, which has almost the same structure as nizatidine, interacts with MBTH in the ratio 1:4 (12). On applying the TLC technique for the developed reaction product of nizatidine with MBTH prepared in the ratio 1:4 exactly it was found that the developed reaction product has only one colored spot which revealed that the product is a single product. No free nizatidine or active coupling species (II) which support the results obtained from the continuous variation method. The reaction of nizatidine sulfoxide with MBTH proceeds in a similar manner to nizatidine since they contain the same reactive centers.

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Optimisation of Variables

Effect of MBTH Concentration

When various concentrations of MBTH solution were added to a fixed concentration of nizatidine, 1 ml of 0.35% of MBTH solution was found enough to develop the color in its full intensity. To ensure an excess of MBTH, 2 ml of 0.35% solution was used for all experiments within the concentration range (1.6–8 $\mu g \cdot ml^{-1}$) of the reaction mixture.

Effect of Oxidising Agents

The optimum color development was found by using 5 ml of 1% ferric chloride solution. Higher concentrations of ferric chloride did not affect the absorption intensity of the chromogen. Other oxidising agents investigated including: ammonium cerium (IV) sulphate, hydrogen peroxide, ferric ammonium sulphate and potassium iodate, were found to be inferior to ferric chloride.

Effect of Reaction Time

A reaction time of 50 minutes at $25 \pm 5^{\circ}C$ is optimum for maximum absorption intensity of the colored nizatidine- MBTH product. To ensure complete reaction, 60 minutes was used as a reaction time for all experiments within the concentration range (1.6–8 $\mu g \cdot ml^{-1}$). The colors obtained were stable for at least 3 hours.

Effect of Diluting Solvent

The dilution of the aqueous solution of the colored reaction product by different solvents e.g. water, methanol, ethanol, acetone, isopropanol, acetonitrile and 0.1 N HCl was studied. It was found that water was the best solvent as it gave the highest absorption reading, moreover its choice adds to the advantages of the method. To obtain higher absorbance avoid the addition of water before the time required for development of the reaction.

Effect of Hydrochloric Acid Concentration

Different concentrations of hydrochloric acid (0.01 N - 4 N) were investigated as a solvent for MBTH and ferric chloride. It was found that the optimum normality of hydrochloric acid was 0.1 N.

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Effect of Temperature on the Reaction Time

Different temperatures (25–100°C) during the reaction time were also studied. It was found that at 25°C ± 5°C the reaction time used was one hour. While at higher temperatures, the maximum absorbance was attained rapidly [As the temperature increases, the reaction time decreases] but the developed color was unstable and decomposed rapidly. So 25°C ± 5°C was chosen as an optimum temperature for the reaction.

Quantification

A linear correlation was found between the absorbance at 613 nm, 651nm and the peak heights of the first derivative spectra at 680 nm and the concentration of nizatidine in the range of (1.6-8 $\mu g \cdot ml^{-1}$) of reaction mixture.

The regression equations were computed and found to be:

$A = 0.00370\ C - 0.0009$	$r = 0.999995$	at 613 nm
$A = 0.00341\ C - 0.0003$	$r = 0.999993$	at 651 nm
$D_1 = 0.01074\ C - 0.0013$	$r = 0.999988$	at 680 nm

Where A is the absorbance at the corresponding wavelength, D_1 is the peak height in cm and C is the corresponding concentration in $\mu g \cdot ml^{-1}$ of the reaction mixture.

The developed color was not extracted in organic solvents such as: n-heptane, butane, hexane, chloroform, methylene chloride and carbon tetrachloride.

Zero-order absorption spectra of the reaction products of nizatidine and its degradation products (i.e., nizatidine amide and nizatidine sulfoxide) with MBTH, show certain overlapping which interfere with the direct spectrophotometric determination of pure nizatidine by the proposed method. This is shown in Figure 1.

The first derivative technique was the answer to this overlapping peak problem (Fig. 2), and it is applicable for the determination of pure nizatidine in laboratory prepared mixtures containing up to 10% of nizatidine amide, and 10% of nizatidine sulfoxide, in combination. The results obtained were compared with those of the official method as shown in Table 1.

Higher recovery percentages of direct measurement at 613 nm and 651 nm than that obtained from the first derivative technique at 680 nm indicate the presence of degradation products while the same recovery percentages at the previous wavelengths indicate purity of the sample.

The proposed method was applied to the quantitative determination of nizatidine in raw material, laboratory prepared mixtures and in pharmaceutical preparations. The results obtained were compared with those obtained from applying the official USP XXIII (1995) method as shown in Tables 1 and 2. The validity of the proposed method was assessed by applying the standard addition technique. The results obtained are shown in Table 3.

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Table 3. Application of Standard Addition Technique to the Analysis of Pharmaceutical Preparations by the Proposed Colorimetric Method

Preparation	Pure Nizatidine Added (μg)	Recovery (%) of Pure Nizatidine		
		Zero-Order Absorption		First Derivative
		at 613 nm	at 651 nm	at 680 nm
Axid 150 capsules	40	99.97	99.98	100.01
B.N. 5 AG 66 A	80	99.89	99.91	99.93
	160	100.04	100.01	99.97
	240	99.83	99.89	99.79
	320	100.21	100.18	100.25
$\bar{X} \pm$ S.D.		99.99 ± 0.15	99.99 ± 0.12	99.99 ± 0.17
Axid 300 capsules	40	99.87	99.91	99.88
B.N. 6 LF 20 E	80	99.98	99.95	99.97
	160	100.21	100.26	100.17
	240	100.29	100.32	100.25
	320	99.96	99.99	99.93
$\bar{X} \pm$ S.D.		100.06 ± 0.18	100.09 ± 0.19	100.04 ± 0.16

$\bar{X}$: Mean.
S.D. : Standard Deviation.

Statistical comparison show no significant difference between the proposed method and the official USP XXIII (1995) method . The proposed method is found to be accurate and precise since the calculated t values and F ratios are less than their corresponding tabulated ones as shown in Table 4.

Table 4. Statistical Comparison Between the Results Obtained by Applying the Proposed Method and the Official USP XXIII 1995 Method for the Determination of Pure Nizatidine

Values	Colorimetric Method			Official Method
	Zero-Order Absoption		First Derivative	
	at 613 nm	at 651 nm	at 680 nm	
Mean	99.83	99.86	100.03	99.87
S.D.	0.14	0.15	0.26	0.13
Variance	0.0196	0.0225	0.0676	0.0169
n	9	9	9	4
F	1.16 (8.85)*	1.33 (8.85)*	4.0 (8.85)*	
Student's t	0.485 (1.796)*	0.155 (1.796)*	1.148 (1.796)*	

*The figures in parentheses are the corresponding theoretical values at (P = 0.05).

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The proposed method can be used as stability indicating method, for the routine work and for quality control analysis of nizatidine in raw material and in its pharmaceutical preparations due to its rapidity, simplicity, and accuracy.

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