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Research Article

Spectral investigation and analytical application of the vinylamino-substituted haloquinone derivatives of Nizatidine and Ranitidine

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ABSTRACT

Studies were carried out, for the first time, to investigate the formation and spectral characteristics of N-vinylamino-substituted haloquinone derivatives of nizatidine and ranitidine. The reactions involved the condensation of N-alkylvinylamine formed from the interaction between the free secondary amino groups in the investigated drugs and acetaldehyde with each of chloranil, bromanil, and 2,3-dichloronaphthoquinone. The experimental conditions affecting the reactions were optimized and the characteristics of the absorption spectra of the formed colored derivatives were established. Under the optimum reaction conditions and at the λ_{max} of the formed derivatives, linear relationships were found between the absorbances and the concentrations of the investigated drugs in a concentration range of 10–250 μg ml^{-1}. The limits of assays detection were 2.61–7.77 μg ml^{-1}. The precisions of the methods were satisfactory; the relative standard deviations were 1.13–1.73%. The proposed methods were successfully applied to the analysis of the studied drugs in pure and pharmaceutical dosage forms with good accuracy; the recovery percentages were 98.1–101.8 ± 0.58–1.57%. The results were compared favorably with those of the official methods.

Keywords: H_2-Receptor Antagonists; Nizatidine, Ranitidine, *N*-Vinylamino-substituted haloquinones; Spectrophotometry; Pharmaceutical analysis.

INTRODUCTION

Nizatidine (NIZ), and ranitidine (RAN) (Fig. 1), are histamine H_2-receptor antagonists. They competitively inhibit the action of histamine on the H_2-receptors of parietal cells and reduce the gastric acid secretion. These drugs are used for the short term treatment of active duodenal and gastric ulcers and the hypersecretory conditions (e.g. Zollinger-Ellison Syndrome). They are more potent in inhibition of gastric acid secretion than other H_2-receptor antagonists and also they are devoid of their anti-androgenic and hepatic microsomal inhibiting side effects (Potter & Hollister, 2001; Martindale, 2002).

The methods reported for determination of NIZ and RAN in pharmaceutical preparations and/or biological fluids include spectrophotometry (Walash, 2002; Amin, 2003; Al-Ghannam & Belal, 2002; Hassan, 2002; Walash, 2004; El-Yazbi, 2003), electrochemical-based methods (Norouzi, 2007), HPTLC (Kelani, 2002), HPLC (Yousef, 2006), capillary electrophoresis (Perez-Ruiz, 2002), and chemiluminometry (Tang, 2007).

Spectrophotometry, because of its inherent simplicity, low cost, and wide availability of the technique in quality control laboratories, is considered the most convenient analytical technique for the analysis of pharma-

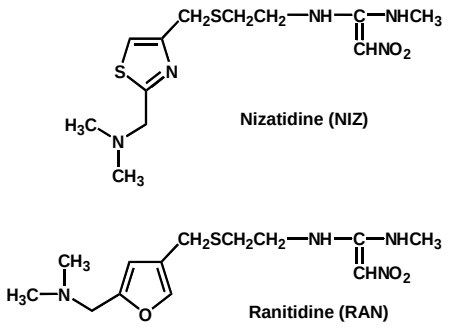

Fig. 1. Chemical structures of nizatidine and ranitidine

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ceuticals in their dosage forms. However, the spectrophotometric methods reported for determination of NIZ and RAN suffer from major disadvantages such as lack of the selectivity (e.g. methods based on oxidation and charge-transfer reactions), laborious extraction procedures for the colored species (e.g. methods based on ion-pair formation), long time for the color development, and/or decreased sensitivity. For these reasons, it was worthwhile to develop new alternative simple, sensitive and more selective spectrophotometric procedures for the determination of NIZ and RAN.

The formation of colored vinylamino-substituted haloquinones derivatives has been demonstrated as a basis for the spectrophotometric determination of of secondary amino group-containing compounds (Darwish, 2005). This color reaction has not been reported yet for NIZ and RAN, therefore, the aim of the present study was directed to investigate the perspective of this color reaction for the spectrophotometric determination of both NIZ and RAN in their bulk and pharmaceutical dosage forms. The analytical procedures involved the reaction NIZ and RAN via their secondary amino groups with acetaldehyde to form of N-alkylvinylamines. These derivatives were then allowed to react with each of chloranil, bromanil, and 2,3-dichloronaphthoquinone (DCNQ) to give colored vinylamino-substituted haloquinone derivatives. These colored products were measured at their λ_{max}. The intensities of the colored products were correlated with the concentrations of the investigated drugs in their sample solutions.

EXPERIMENTAL

Apparatus

A Lambda-3 B (Perkin-Elmer Corporation, Norwalk, USA) and UV-1601 PC (Shimadzu, Kyoto, Japan) ultraviolet-visible spectrophotometers with matched 1-cm quartz cells were used for all measurements.

Reagents and chemicals

Nizatidine (NIZ; Eli Lilly Co, Indianapolis, IN, USA), and ranitidine hydrochloride (RAN; Galaxo-Wellcome, London, UK) were obtained and used as received. Acetaldehyde (Sigma Chemical Co., St. Louis, USA) was 8% (v/v) in propan-2-ol. 2,3,5,6-Tetrachloro-1,4-benzoquinone (chloranil; Sigma Chemical Co, St. Louis, USA), 2,3,5,6-tetrabromo-1,4-benzoquinone (bromanil; Hopkin & Williams Ltd, Essex, UK), and 2,3-dichloronaphthoquinone (DCNQ; Aldrich Chemical, Milwaukee, WI, USA) were 0.8% (w/v) freshly prepared in 1,4-dioxane. All solvents and other chemicals used throughout this study were of analytical grade.

Pharmaceutical dosage forms

The pharmaceutical dosage forms used in the present investigation were the following: Nizatin® capsules (Hi Pharm, Cairo, Egypt) are labeled to contain 300 mg of NIZ per capsule. Ranitidol® tablets (El-Nasr Pharmaceutical Chemicals, Cairo, Egypt) are labeled to contain 150 mg of RAN per tablet. Ranitak® tablets (South Egypt Industries Company, Cairo, Egypt), Zantac® tablets (Galaxo-Wellcome Egypt S.A.E., El-Salaam City, Cairo, Egypt), Ranitidine® tablets (Medical Union Pharmaceuticals, Ismailia, Egypt), and Aciloc® tablets (Sigma, Cairo, Egypt) are labeled to contain 300 mg of RAN per tablet. Zantac® ampoule (Galaxo-Wellcome Egypt S.A.E., Cairo, Egypt), and Ranitidine® ampoule (Medical Union Pharmaceuticals, Ismailia, Egypt) are labeled to contain 50 mg of RAN per ampoule.

Preparation of standard solutions

For NIZ, an accurately weighed amount (150 mg) of NIZ was transferred into a 50-ml volumetric flask. About 25 ml of methanol was added and the contents were shaken well. The volumes were completed to the mark with the same solvent to provide stock standard solutions containing 3 mg ml^{-1}. For RAN, an accurately weighed amount (150 mg) of the ranitidine hydrochloride was dissolved in 10 ml distilled water in 25 ml beaker. The solution was transferred quantitavely into a 100-ml separatory funnel, and the contents of the funnel were made alkaline with 10% NaOH solution. The liberating base was extracted with three 15 ml portions of chloroform. The combined extracts were passed through a small funnel containing 2 g anhydrous sodium sulphate into 50 ml volumetric flask. The content of the separatory funnel was then washed twice with chloroform. The combined extracts and washings were then diluted with same solvent to obtain a working standard solution of 3 mg ml^{-1}, calculated as the hydrochloride salt.

The working standard solutions for both NIZ and RAN were prepared by further dilution with the same solvent to obtain concentrations covering the range of 100-2500 µg ml^{-1}. The solutions were found to be stable for more than one week when kept in the refrigerator.

Preparation of samples of the dosage forms

Tablets and capsules

Twenty tablets or the contents of 20 capsules of each formulation were weighed and finely powdered. A quantity of the mixed powder equivalent to 100 mg of the active component was transferred into a 50-ml calibrated flask, dissolved in 25 ml water, swirled and sonicated for 5 min, completed to volume with water, shaken well for 10 min, filtered, and the first portion of the filtrate was rejected. For NIZ, 25 ml of the filtrate was transferred quantitatively into a 50-ml calibrated flask, completed to the mark with methanol. For RAN, 25 ml of the filtrate was transferred quantitatively into a 50-ml separating funnel then, rendered alkaline with 10% NaOH solution, and the procedure was completed as described for preparation of stock standard RAN solution.

Ampoules

The contents of four ampoules (200 mg of RAN) were quantitatively transferred into a 100-ml calibrated flask, and completed to volume with water, shaken well for 2 min, and filtered if necessary. A 25 ml of the filtrate was transferred quantitatively into a 50-ml separating funnel and the procedure was completed as described for standard RAN solution.

General recommended procedures

One milliliter of the standard or sample solution (100-2500 µg ml^{-1}) was transferred to a 10-ml calibrated flask. One milliliter of acetaldehyde solution (8% v/v, in propan-2-ol) and 1 ml of chloranil, bromanil, or DCNQ reagent solution (0.8%, w/v in 1,4-dioxane) were added. The reaction was allowed to proceed at room temperature (25±5 °C) for 15, 25, and 30 min with chloranil, bromanil, and DCNQ, respectively. The solutions were diluted to volume with propan-2-ol and the absorbances were measured at 685, 652, or 582 nm for NIZ or at 667, 638, or 570 nm for RAN with each of chloranil, bromanil, or DCNQ, respectively, versus a reagent blank treated similarly.

Determination of molar ratio of the reactions

For drugs with acetaldehyde

The Job's method of continuous variation (Job, 1936) was employed. Master equimolar solutions (3×10^{-2} M) of the drugs (NIZ and RAN) and acetaldehyde were used. A series of 5-ml portions of the master solutions of the drugs and acetaldehyde were made up comprising different complimentary ratios (0:10, 1:9, 9:1, 10:0) in 10-ml calibrated flasks. One milliliter of the haloquinone reagent (chloranil, bromanil, and DCNQ) solutions (4×10^{-2} M) were manipulated as described under the general assay procedures described before.

For N-alkylvinylamino derivative of the drugs with haloquinone reagents

The Job's method (Job, 1936) was also employed. Master equimolar solutions (3×10^{-2} M) of the drugs (NIZ and RAN) and the haloquinone reagents were prepared. In 10-ml calibrated flasks, 1 ml of acetaldehyde solution (8% v/v) was transferred. A series of 5-ml portions of the master solutions of the drugs and haloquinone reagent (chloranil, bromanil, and DCNQ) solutions were made up comprising different complimentary ratios (0:10, 1:9, 9:1, 10:0). The reactions were manipulated as described under the general assay procedures.

RESULTS AND DISCUSSION

Involved reaction and spectral characteristics

The reaction involved in the present study was based on the interaction of the free secondary amino group in NIZ and RAN with acetaldehyde forming N-alkylvinylamines. The formed N-alkylvinylamines were then allowed to react with chloranil, bromanil, or

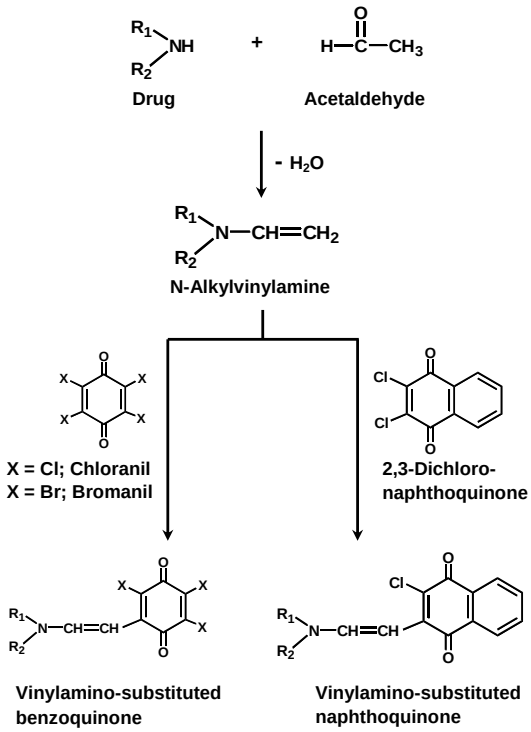

Fig. 2. Scheme for the reaction pathway of one secondary amino group in each of the investigated drugs with acetaldehyde and each of chloranil, bromanil, and DCNQ.

Table. 1. Optimum experimental condition for the proposed spectrophotometric determination of nizatidine and ranitidine via formation of their vinyl-amino substituted quinine derivatives by reaction with acetaldehyde and haloquinone reagents

Experimental condition	Haloquinone reagent		
	Chloranil	Bromanil	DCNQ
Acetaldehyde conc. (%, v/v)[a]	8	8	8
Haloquinone reagent conc. (%, w/v)[a]	0.8	0.8	0.8
Reaction time (min)[a]	15	25	30
Diluting solvent[a]	Propan-2-ol	Propan-2-ol	Propan-2-ol
Maximum absorption peak (nm)			
Nizatidine	685	652	582
Ranitidine	667	638	570

[a] The cited values were used for both nizatdine and ranitidine.

DCNQ to give colored vinylamino-substituted quinones which exhibited absorption maxima at 665, 655, and

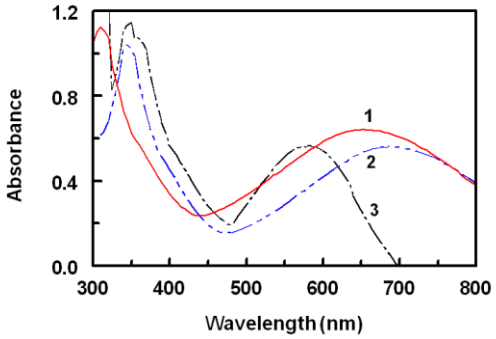

Fig. 3 Absorption spectra of the reaction products of NIZ (120 μg ml^{-1}) with acetaldehyde and each of 1, chloranil; 2, bromanil, and 3, DCNQ.

580 nm with chloranil, bromanil, and DCNQ, respectively. The scheme for the reaction pathway is given in Fig. 2, and the absorption spectra for the reaction products are given in Fig. 3. Three haloquinones were used in this study to investigate their relative reactivity with the investigated drugs, and ultimately the differences in the assay performance parameters.

A previous study (Darwish, 2005) and preliminary experiments in the present investigation showed that free amines gave more sensitive (~ 50 folds) assays than their corresponding hydrochloride salts. For this reason, the reaction of RAN involved in the present study was carried out on the free RAN base, rather than the HCl salt. The following sections describe the optimization of different factors affecting the chemical reaction, and the use of the optimized conditions in the development of the assay procedures.

Optimization of reaction conditions

The effects of variables affecting the reactions (concentrations of acetaldehyde and haloquinone reagent, reaction time, temperature, and the diluting solvent) were performed by altering each variable in turn while keeping the others constant. The color development was studied as a function of the concentrations of acetaldehyde and haloquinone reagent. The results indicated that the color development was dependent on both acetaldehyde and haloquinone reagent. The highest color intensity was attained when the concentration of acetaldehyde was 8%, v/v and the concentration of haloquinone reagent was 0.8 %, w/v.

The results obtained from the optimizing of the reaction time indicated that complete color development was attained at room temperature (25±5°C) after 15, 25, and 30 min in cases of bromanil, chloranil, and DCNQ, respectively. Increasing temperature had a significant and rapid negative effect on the color formation. Therefore, further experiments were carried out at room temperature. The absorbance of the colored products for both drugs remained stable for at least 40 min which gave the advantage of comfortable measuring at any time within that period without any change in absorbance intensity. The aforementioned data were presented for the reaction of NIZ, and similar reaction profiles were obtained with RAN.

In order to select the most appropriate solvent for dilution, different solvents were tested: methanol, ethanol, propanol, acetone, acetonitrile, propan-2-ol, and 1,4-dioxane. The highest color intensity was obtained when propan-2-ol was used as a diluting solvent, and therefore it was selected for further investigations. The aforementioned data were presented for the reaction of NIZ, and similar reaction profiles were obtained with RAN. A summary for the optimum conditions for the reactions of both NIZ and RAN are given in Table 1.

Determination of the molar ratio of the reactants

The results of investigating the molar ratios of the reactions revealed that the ration of drug:acetaldehyde was 1:2 (i.e. one mole of drug reacts with 2 moles of acetaldehyde) for both NIZ and RAN. This ratio indicated that the two secondary amino groups in each drug molecule were reactive and formed the N-alkylvinylamino derivative of each drug. Each molecule of the formed N-alkylvinylamino derivative condensed with two molecules of the haloquinone reagent.

Validation of the proposed methods

Linearity and sensitivity

Under the specified optimum reaction conditions (Ta-

Table. 2. Quantitative parameters for the proposed spectrophotometric methods for analysis of nizatidine and ranitidine by reaction with acetaldehyde and various haloquinone reagents

Parameter	Nizatidine			Ranitidine		
	Chloranil	Bromanil	DCNQ	Chloranil	Bromanil	DCNQ
Range (μg/ml)	35-150	20-130	45-220	30-195	25-170	60-250
Intercept (a)	0.0011	-0.0009	-0.0011	0.0048	-0.0162	-0.0011
Slope (b)	0.0052	0.0090	0.0040	0.0042	0.0030	0.0040
Correlation coefficient (r)	0.9997	0.9991	0.9982	0.9985	0.9995	0.9991
Molar absorptivity (ε, l mol^{-1} cm^{-1})	1852	2385	1245	1575	1880	1166
LOD (μg ml^{-1})	2.61	2.95	7.51	3.43	2.89	7.77
LOQ (μg ml^{-1})	7.83	8.81	22.52	10.2	8.60	23.32

ble 1), the calibration curves for NIZ and RAN with the three haloquinone reagents employed in the present work were constructed by analyzing a series of concentrations of the standard solutions of the drugs. The assay was performed according the established general recommended procedures. The regression equations for the results were derived using the least-squares method. In all cases, Beer's plots (n = 5) were linear with very small intercepts and good correlation coefficients in the general concentration range of 10-250 μg ml^{-1} (Table 2). The limits of detection (LOD) and limits of quantitation (LOQ) were determined using the formula: LOD or LOQ = κSDa/b, where κ = 3 for LOD and 10 for LOQ, SDa is the standard deviation of the intercept, and b is the slope. Based on the basis of 5 replicate measurements, the LOD and LOQ values were 2.61–7.77 and 7.83–23.32 μg ml^{-1}, respectively. The results indicated that chloranil and bromanil gave relatively higher sensitivities (ε values) than DCNQ. The lower sensitivities obtained with DCNQ were attributed to the limiting steric factors due to its bulky molecular structure than chloranil and bromanil (Rosenblatt & Burrows, 1982).

Precision

The precisions of the assays were determined by replicate analysis of five separate sample solutions of the working standards at three concentration levels of each compound. The assays gave satisfactory results; the relative standard deviations (RSD) were less than 2%. This level of precision of the proposed methods is adequate for the quality control analysis of the investigated compounds in their pharmaceutical dosage forms.

Interference studies

Before analyzing the investigated drugs in their pharmaceutical dosage forms, interference liabilities were performed to explore the effect of common excipients that might be added during formulations. Samples were prepared by mixing known amount of the drug with various amounts of the common excipients: starch, sucrose, lactose, glucose, magnesium stearate, gum acacia, talc, and ascorbic acid (added as stabilizer in the formulation of the ampoule). The analysis of these laboratory-prepared samples was performed using the general recommended procedure, and the recovery values were determined. The results indicated that there was no interference from the used excipients; the recovery values were 98.3–100.5 ± 0.38–1.70%. This indicated the absence of interference liabilities from these excipients.

Robustness and ruggedness

Robustness was examined by evaluating the influence of small variation in the experimental parameters; concentration of the analytical reagents and time on the method performance. In these experiments, one parameter was changed while the others were kept unchanged, and the recovery percentage was calculated each time. It was found that none of these variables significantly affect the method. This provided an indication for the reliability of the proposed method during its routine application for analysis of the investigated

Table. 3. Analysis of nizatidine and ranitidine in their dosage forms by the proposed spectrophotometric methods

Drug / dosage form	Recovery (% ± SD) [a]			
	Chloranil	Bromanil	DCNQ	Official [b]
Nizatidine				
Nizatin capsules	99.5 ± 0.80 (2.44, 2.06)	98.5 ± 0.90 (1.92, 0.55)	98.5 ± 0.80 (2.34, 0.76)	98.1 ± 1.25
Ranitidine				
Ranitidine tablets	98.5 ±1.46 (3.89, 0.33)	100.5 ± 1.16 (2.45, 2.72)	99.5 ±0.86 (1.33, 1.88)	98.4 ± 0.74
Zantac tablets	99.5 ± 1.48 (3.5, 2.33)	99.7 ± 1.29 (2.59, 2.83)	98.5 ± 0.71 (1.24, 2.48)	97.3 ± 0.79
Ranitak tablets	99.0 ± 1.37 (3.90, 1.66)	100 ± 1.42 (4.22, 2.56)	98.1 ± 1.17 (2.73, 0.67)	97.6 ± 0.69
Ranitidol tablets	99.3 ± 1.21 (1.53, 2.29)	98.3 ± 1.11 (1.83, 1.29)	99.8 ± 1.31 (1.31, 2.66	97.2 ± 1.50
Zantac ampoule	101.5 ± 1.53 (1.49, 1.38)	101.3 ± 1.03 (1.47, 1.78)	101.8 ± 0.58 (4.64, 2.38)	100.1 ± 1.25
Ranitidine ampoule	100.6 ± 1.33 (3.36, 2.49)	100 ± 1.33 (3.31, 1.64)	99.2 ± 1.03 (1.99, 0.88)	98.6 ± 0.73
Aciloc tablets	100.1 ± 1.57 (3.61, 1.90)	99.8 ± 0.67 (1.49, 2.17)	100 ± 0.69 (1.99, 0.88)	98.8 ± 0.82

a. Values are mean of five determinations
b. Reference: British Pharmacopoeia, 1998.
c. Figures in parenthesis are the calculated values of t and F; the tabulated values at 95% confidence limit are 2.78 and 6.39, respectively.

drugs. Ruggedness was also tested by applying the proposed method to the assay of both NIZ and RAN using the same procedure but using two different instruments at two different laboratories and different elapsed time. The results obtained from lab- to-lab and day-to-day variations were found to be reproducible, as RSD did not exceed 2%.

Analysis to the analysis of pharmaceutical dosage forms

The available pharmaceutical dosage forms of the investigated drugs were subjected to their analysis by the proposed, as well as the official methods (British Pharmacopoeia, 1998) and the obtained results were statistically compared with each other. The mean percentage recoveries, relative to the labelled amounts, obtained by the proposed methods ranged from 98.1–101.8 ± 0.58–1.57% (Table 3). With respect to the accuracy (t-test) and precision (F-test), no significant differences were found between the calculated and theoretical values of both the proposed and the reported methods at 95% confidence level. This indicated similar accuracy and precision in the analysis of the investigated compounds in their pharmaceutical dosage forms. It worth to mention that the proposed methods have the advantage of the specificity because the measurements are performed in the visible region, away from the UV-absorbing substances that might be co-extracted from the dosage forms.

CONCLUSIONS

The present study investigated the formation of vinylamino-substituted haloquinone derivatives of NIZ and RAN by their reaction with chloranil, bromanil, and DCNQ in presence of acetaldehyde. The formation of these colored derivatives was used as a basis in the development of three spectrophotometric methods for the determination of NIZ and RAN. These methods were simple, rapid, accurate, and reliable for the determination of both drugs in their pharmaceutical dosage forms without interference from the common excipients. The proposed methods can be used in quality control laboratories for the analysis of the investigated drugs because of their simplicity, sufficient sensitivity, low-cost, and their independence on expensive and/or critical analytical reagents.

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