Acta Pharm. 58 (2008) 87–97
10.2478/v10007-007-0047-z

Original research paper

A sensitive spectrophotometric method for the determination of H_2-receptor antagonists by means of *N*-bromosuccinimide and *p*-aminophenol

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A simple, accurate and sensitive spectrophotometric method for determination of H_2-receptor antagonists: cimetidine (CIM), famotidine (FAM), nizatidine (NIZ), and ranitidine hydrochloride (RAN) has been fully developed and validated. The method was based on the reaction of these drugs with NBS and subsequent measurement of the excess *N*-bromosuccinimide by its reaction with *p*-aminophenol to give a violet colored product (λ_{max} at 552 nm). Decrease in the absorption intensity (ΔA) of the colored product, due to the presence of the drug, was correlated with its concentration in the sample solution. Different variables affecting the reaction were carefully studied and optimized. Under optimal conditions, linear relationships with good correlation coefficients (0.9988–0.9998) were found between ΔA values and the corresponding concentrations of the drugs in a concentration range of 8–30, 6–22, 6–25, and 4–20 μg mL^{-1} for CIM, FAM, NIZ, and RAN, respectively. Limits of detection were 1.22, 1.01, 1.08, and 0.74 μg mL^{-1} for CIM, FAM, NIZ, and RAN, respectively. The method was validated in terms of accuracy, precision, ruggedness, and robustness; the results were satisfactory. The proposed method was successfully applied to the analysis of the above mentioned drugs in bulk substance and in pharmaceutical dosage forms; percent recoveries ranged from 98.5 ± 0.9 to 102.4 ± 0.8% without interference from the common excipients. The results obtained by the proposed method were comparable with those obtained by the official methods.

Keywords: H_2-receptor antagonists, *N*-bromosuccinimide, *p*-aminophenol, spectrophotometry, pharmaceutical analysis

Accepted December 11, 2007

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Histamine H_2-receptor antagonists (H_2-RAs) competitively inhibit the action of histamine on the H_2-receptors of parietal cells and thereby reduce the gastric acid secretion under daytime and nocturnal basal conditions. H_2-RAs are used for short-term treatment of active duodenal ulcer, active and benign gastric ulcer, pathogenic gastrointestinal hypersecretory conditions (*e.g.*, Zollinger-Ellison syndrome), and short-term symptomatic relief of gastroesophageal refluxes (1). H_2-RAs include cimetidine (CIM), famotidine (FAM), nizatidine (NIZ) and ranitidine hydrochloride (RAN); their chemical structures are given in Fig. 1.

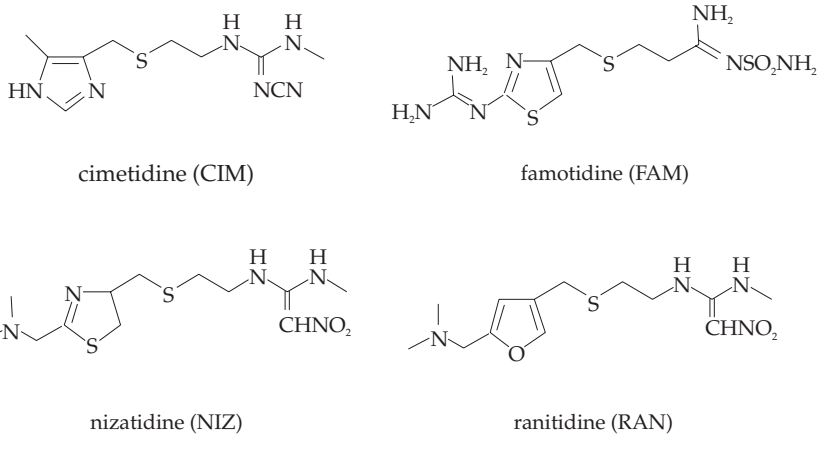


Fig. 1. Chemical structures of the investigated H_2-receptor antagonists (H_2-RAs).

Because of the therapeutic importance of H_2-RAs, several methods have been reported for their determination in bulk, pharmaceutical dosage forms, and/or biological fluids. These methods include titrimetry (2), electrochemical methods (3), TLC (4), HPLC (5, 6), capillary electrophoresis (7), immunoassay (8), fluorimetry (9, 10), and spectrophotometry (11–17).

N-haloimides have been used as effective oxidizing/brominating agents for the spectrophotometric determination of many pharmaceutical compounds (18, 19). *N*-bromosuccinimide (NBS), being the most versatile, is the most commonly used haloimide (20–22). The analysis involving NBS was based on direct measurement of the chromogenic derivative of the drug, or indirectly by measuring the remaining NBS with color-producing reagents susceptible to oxidation or bromination with NBS.

It was reported that *p*-aminophenol (PAP) is easily susceptible to oxidation with NBS and gives a violet chromogenic product of λ_{max} at 552 nm (23). The use of NBS/PAP combination has not been investigated in the spectrophotometric determination of H_2-RAs. The present study describes, for the first time, the use of a NBS/PAP combination in the development of a new simple spectrophotometric method for determination of H_2-RAs. The analytical procedure involved oxidation of H_2-RAs with excess NBS and

subsequent measurement of the remaining unreacted NBS by its reaction with PAP to give a violet colored product that was measured at 552 nm. The decrease in the absorption intensity (ΔA) at 552 nm, caused by the presence of the drug, was directly proportional to the amount of the drug in the sample solution.

EXPERIMENTAL

Apparatus

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

Materials and reagent solutions

Cimetidine and famotidine (Sigma Chemical Co., USA), nizatidine (Eli Lilly Co, USA), and ranitidine hydrochloride (Glaxo-Wellcome, UK) were obtained and used as received. Stock standard solutions (0.2 mg mL^{-1}) were prepared. Working standard solutions were obtained by further dilution of the stock solution with water. *N*-bromosuccinimde (Merck, USA) was 0.15% (*m/V*) aqueous solution prepared fresh daily. *p*-Aminophenol (Laba Chemie PVT Ltd., India) was 0.2% (*m/V*) prepared fresh daily by dissolving PAP in 1.5% (*V/V*) hydrochloric acid. All solvents, acids, and other chemicals used throughout the study were of analytical grade. Doubly distilled water was obtained through a Nanopure II water purification system (Barnstead/Thermolyne, USA) and was used throughout the work.

Pharmaceutical formulations

Famotin® tablets (Memphis, Egypt), Antodine® tablets (Amoun Pharmaceutical Industries, Egypt), Servipep® tablets (Novartis Pharma, Egypt), Peptic tablets (Julphar, UAE), Famotak® tablets (South Egypt Industries Company, Egypt), Gastrodomina® tablets (Medical Union Pharmaceuticals, Egypt), and Antodine® ampoules (Amoun Pharmaceutical Industries, Egypt) are labeled to contain 40 mg of FAM per tablet or ampoule. Nizatin® capsules (Hi Pharm, Egypt) are labeled to contain 300 mg of NIZ per capsule. Ranitidol® tablets (El-Nasr Pharmaceutical Chemicals, Egypt) are labeled to contain 150 mg of RAN per tablet. Ranitak® tablets (South Egypt Industries Company, Egypt) are labeled to contain 300 mg of RAN per tablet. Zantac® tablets (Glaxo-Wellcome Egypt, Egypt), and Ranitidine® tablets (Medical Union Pharmaceuticals, Egypt), Aciloc® tablets (Sigma, Egypt) are labeled to contain 300 mg of RAN per tablet. Zantac® ampoule (Glaxo-Wellcome Egypt) and Ranitidine® ampoule (Medical Union Pharmaceuticals) are labeled to contain 50 mg of RAN per ampoule. Cimetidine tablets were simulated in the laboratory according to the reported formulation and were labeled to contain 300 mg of CIM per tablet.

General recommended procedure

One milliliter of the standard or sample solution containing 40–350 μg mL^{-1} of the active material was transferred into a 10-mL calibrated flask. One milliliter of NBS solution (0.15%, *m/V*) was added, and the reaction was allowed to proceed at room temperature (25 ± 5 °C) for 15 min. One milliliter of HCl acid (1.5%, *V/V*) and 1 mL of PAP (0.2%, *m/V*) were added. The contents of the flask were mixed and allowed to stand at room temperature (25 ± 5 °C) for 5 min. The reaction mixtures were made up to volume with water and absorbances were measured at 552 nm against blank solutions prepared in the same manner without the drug. For direct measuring of the decrease in the absorbance intensity (ΔA values), the positions of the cuvettes for the blank and sample were exchanged. Calibration graphs were constructed by plotting the ΔA values *vs.* the corresponding drug concentration, and the amount of the drug in each particular sample was calculated from its corresponding calibration curve.

Determination of accuracy by the standard addition method

The accuracy of the proposed method was evaluated by addition of varying amounts of the authentic materials. Three concentrations were added for each analyte; 5.0, 15.0 and 25.0 mg were added for CIM and NIZ, whereas 2.5, 7.5 and 17.5 mg were added for FAM and RAN to a dosage form containing a fixed amount of the active ingredient, and the recovery percentage was determined for the added amount. Cimetidine, Servipep, and Zantac tablets as well as Nizatin capsules were used for the standard addition method.

Interferences study

Samples were prepared by mixing a known amount (300 mg) of CIM with common excipients: lactose, sucrose, starch, magnesium stearate, and ascorbic acid (added as stabilizer in the formulation of the ampoule). The mass ratios were 3, 12, 6, 60, and 15 for lactose, sucrose, starch, magnesium stearate, and ascorbic acid, respectively. The analysis of these laboratory-prepared samples was carried out using the general recommended procedure, and the recovery values were determined.

Analysis of dosage forms

Tablets and capsules. – Twenty tablets or the contents of 20 capsules were weighed and finely powdered. An accurately weighed quantity of the powdered tablet or capsule contents equivalent to 200 mg of the active ingredient was transferred into a 100-mL calibrated flask and dissolved in about 50 mL of water. The contents of the flask were swirled, sonicated for 5 min, and then made up to the volume with water. The mixtures were mixed well, filtered and the first portion of the filtrate was rejected. Prepared solution was diluted 100 times and the resulting solution was used for analysis by the recommended procedure.

Ampoules. – The contents of five ampoules were quantitatively transferred into a 250-mL calibrated flask, made up to the mark with water, and the resulting solution was used for analysis by the recommended procedure.

Determination of molar ratio of the reactants by the mole ratio method

H_2-RAs with NBS. – One-milliliter aliquots of the drug solution (6.6×10^{-3} mol L^{-1}) were transferred into 25-mL calibrated flasks. To each flask, 1–10-mL aliquots of NBS solution (6.6×10^{-3} mol L^{-1}) were added, and the reactions were allowed to proceed for 15 min at room temperature (25 ± 5 °C). One milliliter of hydrochloric acid (1.5%, *V/V*) and 1 mL of PAP solution (0.2%, *m/V*) were added to each flask. The reaction mixtures were allowed to stand at room temperature for 5 min and were made up to volume with water. The ΔA values were measured as described under the general recommended procedure.

NBS with PAP. – One-milliliter aliquots of NBS solution (6.6×10^{-3} mol L^{-1}) were transferred into 25-mL calibrated flasks. To each flask, 1 mL of hydrochloric acid (1.5%, *V/V*), and 1–10-mL aliquots of PAP solution (6.6×10^{-3} mol L^{-1}) were added. The reactions were allowed to proceed for 5 min at room temperature (25 ± 5 °C) and were then made up to volume with water. The absorbance was measured at 552 nm against reagent blanks prepared without NBS.

RESULTS AND DISCUSSION

Optimum conditions

The proposed procedures using NBS and PAP involved two steps; the first involved treatment of the investigated H_2-RAs with a known excess amount of NBS, the second step involved determination of the remaining unreacted NBS *via* its reaction with PAP reagent. The decrease in the absorption intensity (ΔA) at 552 nm, caused by the presence of the drug, was directly proportional to the amount of the drug in its sample solution. Fig. 2 illustrates the absorption spectra of the reaction product of NBS with PAP in the presence and in the absence of cimetidine, as a representative example of H_2-RAs. Similar patterns were obtained with other H_2-RAs.

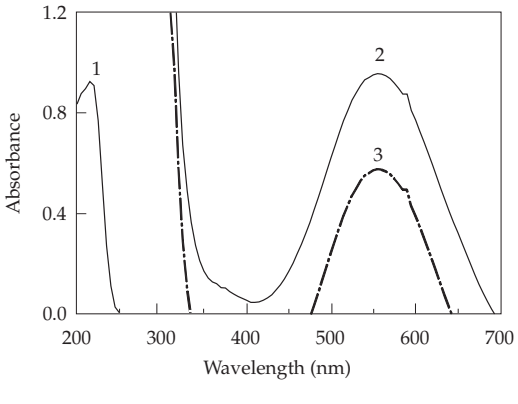


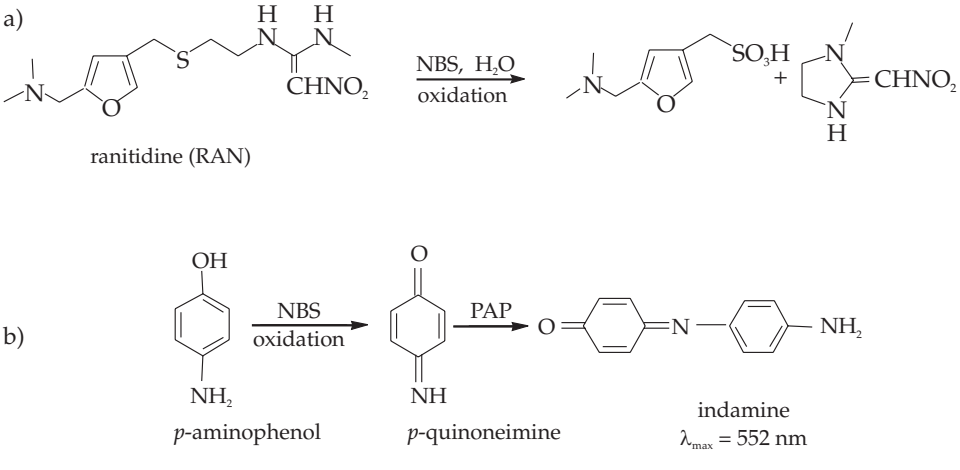
Fig. 2. Absorption spectra of: 1) cimetidine (20 μg mL^{-1}), 2) reaction product of NBS (0.15%, *m/V*) and PAP (0.2%, *m/V*) in the absence of cimetidine, and 3) the reaction from 2) in the presence of cimetidine (20 μg mL^{-1}).

The optimum NBS concentration was found to be 0.15% (*m/V*). The reaction between H_2-RAs and NBS was found to proceed in neutral medium. However, for complete reaction between NBS and PAP, acidic medium was necessary. The highest ΔA values were obtained when hydrochloric acid was used; the optimum concentration of hydrochloric acid at which the maximum readings were obtained was 1.5–2% (*V/V*). The results revealed that the reaction was completed within 10–20 min at room temperature (25 ± 5 °C). For more precise reading, the measurements were carried out after 15 min.

Different solvents were tested in order to select the most appropriate solvent for dilution. Although the highest readings were obtained when methanol was used, water was preferred for economic reasons and safe-environment considerations. After dilution with water, the ΔA values were found to be stable for at least 60 min.

Stoichiometry and the mechanism

The study of the stoichiometry for the reaction between the investigated H_2-RAs and NBS revealed that the drug/NBS ratio was 1:4 in all cases (*i.e.*, 1 mole of the drug reacted with 4 moles of NBS). The molar ratio for the reaction between NBS and PAP was found to be 4:1. Based on these findings, the reactions of ranitidine with NBS and NBS with PAP were assumed to proceed according to the pathway given in Scheme I.



Scheme 1

Validation of the method

Linearity, limits of detection and quantitation. – In all cases, Beer's law plots (n = 5) were linear with good correlation coefficients (0.9988–0.9998) in the general concentration ranges of 8–30, 6–22, 6–25, and 4–20 μg mL^{-1} for CIM, FAM, NIZ, and RAN, respectively (Table I). Amin *et al*. (12, 13) reported the range of 0.1–2.6 μg mL^{-1}. The limits of detec-

tion (*LOD*) and limits of quantitation (*LOQ*) were determined (24) using the formula: *LOD* or *LOQ* = $\kappa SD_a/b$, where κ = 3.3 for *LOD* and 10 for *LOQ*, SD_a is the standard deviation of the intercept, and b is the slope. The *LOD* and *LOQ* values ranged from 0.74–1.22 and 2.25–3.69 μg mL^{-1}, respectively (Table I).

Precision. – The precision (repeatability) of the method was determined by replicate analysis of five separate solutions of the working standards at three concentration levels of each drug. Relative standard deviations were 0.8, 0.9, 0.9, and 1.2 for CIM, FAM, NIZ, and RAN, respectively (Table I) indicating good precision of the proposed methods.

Interferences. – The results of the interferences study showed that no interference was found from lactose, sucrose, starch, talc, gum acacia, glucose, and magnesium stearate; the recovery of CIM was 99.3–100.7%. This indicated the absence of interferences from these excipients. On the other hand, ascorbic acid was found to interfere with the assay procedure. This interference could be eliminated by adding 1 mL of 0.1% (*m/V*) aqueous solution of potassium bromate to the ampoule samples prior to their analysis. Potassium bromate, being a mild oxidant, was used in this experiment to oxidize the ascorbic acid; however, it was unable to oxidize the drug (RAN). This gave an important advantage to the proposed method over the method reported by Amin *et al.* (12, 13) who did not investigate that interference.

Robustness and ruggedness. – Robustness was examined by evaluating the influence of a small variation of the method variables including the concentration of analytical reagents and reaction time on the performance of the proposed methods. In these experiments, one parameter was changed whereas the others were kept unchanged, and the recovery percentage was calculated each time. It was found that small variations in these variables did not affect the method significantly. This was an indication of the reliability of the proposed method during its routine application for analysis of the investigated drugs. Ruggedness was tested by applying the proposed methods to the assay of

Table I. Analytical parameters for the analysis of H_2-RAs drugs by the proposed spectrophotometric method

Parameter	CIM	FAM	NIZ	RAN
Linear range (mg mL^{-1})	8–30	6–22	6–25	4–20
Intercept	0.0043	0.0080	0.0390	0.0026
Slope	0.0222	0.0355	0.0295	0.0400
Correlation coefficient	0.9989	0.9998	0.9995	0.9988
$\varepsilon \times 10^3$ (L mol^{-1} cm^{-1})	6.710	11.960	10.060	16.100
LOD (μg mL^{-1})	1.22	1.01	1.08	0.74
LOQ (μg mL^{-1})	3.69	3.06	3.28	2.25
Ruggedness (RSD, %)	0.84	0.73	1.06	0.85
Repeatability (RSD, %)	0.81	0.88	0.92	1.22
Recovery (%)[a]	99.8–100.2	99.9–101.2	99.7–100.5	98.8–99.6

[a] Values are the mean of three determinations.

the investigated drugs using the same operational conditions but using two different instruments in two different laboratories and different elapsed time. Results obtained from lab-to-lab and day-to-day variations were found to be reproducible, the full range of recovery values was 98.4–101.3% and the RSD was 0.8, 0.7, 1.1, and 0.9% for CIM, FAM, NIZ and RAN, respectively (Table I).

Accuracy and application of the proposed method to analysis of dosage forms

The accuracy of the proposed method was evaluated by recovery studies using the standard addition method. The obtained recovery values were 99.8–100.2, 99.9–101.2, 99.7–100.5, and 98.8–99.6% for CIM, FAM, NIZ, and RAN, respectively (Table I). This indicated high accuracy of the proposed method.

It is evident from the aforementioned results that the proposed method gave satisfactory results with the investigated drugs in bulk. Their pharmaceutical dosage forms were subjected to the analysis of the active ingredient by the proposed method and the official titrimetric method stated in the British Pharmacopoeia (25). The label claim, as percentage, ranged from 98.5–102.4% (Table II). These results were compared with those

Table II. Analysis of H_2-receptor anatogonist drug-containing dosage forms by the proposed and official methods

Product	Label claim (%)[a]		*t*-value[b]	*F*-value[b]
	Proposed method	Official method[c]		
Cimetidine® tablets	100.3 ± 0.9	98.9 ± 0.6	2.20	2.43
Famotine® tablets	101.3 ± 0.9	99.3 ± 0.7	2.06	1.66
Servipep® tablets	102.1 ± 1.7	100.6 ± 1.2	2.05	1.71
Peptic® tablets	98.5 ± 1.0	97.2 ± 1.5	2.34	1.44
Famotak® tablets	100.9 ± 1.0	99.4 ± 0.7	2.22	2.03
Antodine® tablets	99.5 ± 0.8	98.6 ± 0.7	1.08	1.29
Gastrodomina® tablets	100.5 ± 1.1	99.2 ± 0.7	2.41	1.95
Antodine® ampoules	102.4 ± 0.8	101.5 ± 0.6	1.87	1.63
Nizatin® capsules	99.6 ± 1.8	98.1 ± 1.3	2.19	1.72
Ranitidine® tablets	99.9 ± 0.8	98.4 ± 0.7	2.41	0.66
Zantac® tablets	98.8 ± 1.3	97.3 ± 0.8	2.70	1.95
Ranitak® tablets	99.7 ± 1.1	97.6 ± 0.7	2.23	2.13
Ranitidol® tablets	98.5 ± 1.1	97.2 ± 1.5	1.73	1.63
Aciloc® tablets	99.6 ± 1.1	98.7 ± 0.8	1.83	1.38
Zantac® ampoules	101.8 ± 1.6	100.1 ± 1.3	1.71	1.92
Ranitidine® ampoules	99.8 ± 0.8	98.6 ± 0.7	1.18	1.70

[a] Values are mean ± SD, $n = 5$.
[b] Theoretical values for t and F at 95% confidence limit and $n = 5$ were 2.78 and 6.39, respectively.
[c] Reference 25.

obtained from the official method by statistical analysis. No significant differences were found between the calculated and theoretical values of *t*- and *F*-tests at 95% confidence level proving comparable accuracy and precision in the analysis of the investigated drugs in their dosage forms.

CONCLUSIONS

The results demonstrated the usefulness of the NBS-PAP system in the spectrophotometric determination of H_2-receptor antagonists. The proposed method was advantageous over the previously reported spectrophotometric methods in terms of simplicity, selectivity and applicability to analysis of four H_2-RAs.

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S A Ž E T A K

Osjetljiva spektrofotometrijska metoda za određivanje antagonista H_2-receptora uz uporabu *N*-bromsukcinimida i *p*-aminofenola

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Razvijena je i validirana ispravna, jednostavna i osjetljiva spektrofotometrijska metoda za određivanje antagonista H_2-receptora: cimetidina (CIM), famotidina (FAM), nizatidina (NIZ) i ranitidin hidroklorida (RAN). Metoda se temelji na reakciji tih ljekovitih tvari s *N*-bromsukcinimidom (NBS). Višak *N*-bromsukcinimida određuje se nakon reakcije s *p*-aminofenolom s kojim daje ljubičasti produkt (λ_{max} pri 552 nm). Smanjenje apsorpcijskog intenziteta (ΔA) obojenog produkta, zbog prisutnosti ljekovite tvari korelirano je s njegovom koncentracijom u otopini uzorka. Proučavane su različite varijable koje utječu na reakciju. Linearno koncentracijsko područje za CIM, FAM, NIZ i RAN, s koeficijentom korelacije od 0,9988 do 0,9998, iznosi 8–30, 6–22, 6–25 odnosno 4–20 μg mL^{-1}. Granice detekcije bile su 1,23, 1,02, 1,09 i 0,75 g mL^{-1} za CIM, FAM, NIZ, odnosno RAN. Predložena metoda je uspješno primijenjena za analizu navedenih ljekovitih tvari i ljekovitih pripravaka. Nepreciznost od 0,7 do 1,2% i visoka ispravnost (analitički povrat između 98,5 i 102,4%), bez interferencije uobičajenih pomoćnih tvari, ukazuju na dobru analitičku metodu. Rezultati dobiveni predloženom metodom usporedivi su s rezultatima dobivenim službenom metodom.

Ključne riječi: antagonisti H_2-receptora, *N*-bromsukcinimid, *p*-aminofenol, spektrofotometrija, farmaceutska analiza

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