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Voltammetric and Spectrophotometric Determination of Nizatidine in Pharmaceutical Formulations

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Abstract. Two methods are described for quantitative determination of nizatidine. The first is a cathodic stripping voltammetric method which is based on the accumulation of the compound at the hanging mercury drop electrode. The adsorptive stripping response was evaluated with respect of accumulation time, potential, concentration, pH and other variables. A linear calibration graph was obtained over the range $3.0 \times 10^{-8} - 1.0 \times 10^{-6}$ M with a detection limit 3.0×10^{-8} M after a 20s accumulation time at -0.2 V accumulation potential. On the other hand, it was found that the detection limit could be lowered to 1.0×10^{-8} M after 180s accumulation time at -0.2 V accumulation potential. The relative standard deviation was in the range 1.2−2.0% for six measurements. The tolerance amounts of the common excipients have also been reported.

The second is a spectrophotometric method which is based on the formation and extraction of the ion-pair complex formed between nizatidine and either bromocresol green or bromothymol blue. The extracted colored ion-pair complexes absorb at 416 nm. The effect of different factors such as: type of organic solvent, pH, reagent concentration, number of extraction times, shaking time, temperature and the tolerance amount of the common excipients have been reported. The calibration graph was linear in the range $6.0 \times 10^{-7} - 1.8 \times 10^{-5}$ M with a detection limit of 6.0×10^{-7} M and molar absorptivity of 2.1×10^{4} l·mol^{-1} · cm^{-1} when using bromocresol green, while the calibration graph was linear in the range $3.0 \times 10^{-7} - 1.1 \times 10^{-5}$ M with a detection limit of 3.0×10^{-7} M and molar absorptivity of 3.2×10^{4} l·mol^{-1} · cm^{-1} when using bromothymol blue. The spectrophotometric methods offer alternative methods with reasonable sensitivity, selectivity and accuracy with relative standard deviation in the range 2.1−6.0% and 1.2−4.7% (for six measurements) when using bromothymol blue and bromocresol green, respectively. The proposed two methods were applied for the determination of nizatidine in commercially available dosage forms. A comparison between the voltammetric and the extraction-spectrophotometric methods was also reported.

Key words: Voltammetry; spectrophotometry; nizatidine determination.

Nizatidine is N-[2-[[[2-[(dimethylamino)-methyl]-4-thiazolyl]methyl]thio]ethyl]-N-methyl-2-nitro-1, 1-ethylenediamine and belongs to the new generation of anti-ulcer agents. Nizatidine (NIZ) is known to be more potent than cimetidine and effective in the treatment of gastric acid and duodenal ulcerous [1]. Several methods have been reported for the determination of NIZ in pharmaceutical formulations and biological fluids including HPLC [2–4], spectrophotometric [5, 6], coulometric [7], potentiometric titration [8] and polarography [9].

There is a great interest in determining small amounts of NIZ, without use of complicated chemical transformation. The chemical properties of NIZ make possible various chemical reactions and, therefore, it was necessary to select the most suitable conditions for the determination of this compound.

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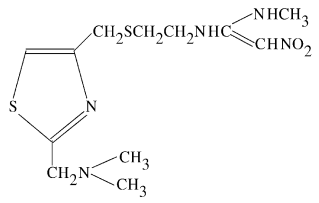

Nizatidine

A survey of the literature reveals that there is only one paper focused on the differential-pulse polarographic determination of NIZ at the droping mercury electrode [9]. No attempts have been made to study the voltammetric behavior of NIZ, where, the adsorptive stripping voltammetry has been widely applied for trace determinations of various categories of drugs [10–13]. Stripping methods for organic compounds make use of a preconcentration step of the analytical species on a suitable working electrode. The preconcentration step can involve direct adsorption of the organic compound or its accumulation as a metal complex or salt.

The aim of the present investigation is to study the adsorptive voltammetric behavior of NIZ in order to develop a new voltammetric method for its determination. The adsorption of NIZ at the mercury electrode surface allowed to develop a procedure with high sensitivity for the determination of low level of NIZ using differential-pulse adsorptive cathodic stripping voltammetry (DP-AdCSV) at a hanging mercury drop electrode (HMDE).

On the other hand, our study of the formation and extraction behavior of the ion-pair complex of NIZ with either bromocresol green (BCG) or bromothymol blue (BTB) showed that new spectrophotometric methods for NIZ determination could be developed.

The obtained results showed that the proposed voltammetric and spectrophotometric methods for determination of NIZ provide high accuracy, precision and sensitivity. Our literature survey showed that there is no official method listed in the pharmacopeias for the determination of NIZ. Therefore the proposed methods can be recommended as official methods of NIZ determination for raw material or in dosage forms.

Experimental

Apparatus

Differential-pulse voltammetry was carried out using EG&G 264A voltammetric analyzer with a model 303A stand operated with the hanging mercury drop electrode (HMDE). The three electrode system was completed using a platinum auxiliary electrode and an Ag/AgCl reference electrode. A Pye-Unicam UV-visible spectrophotometer, model UV-2 was used for spectrophotometric measurements. The cells used for measurements were 1×1 cm quartz cells. A Hanna 8521 model pH meter was used for pH measurements.

Reagents and Materials

Nizatidine (CAS No. 76963-41-2) was kindly supplied by Eli Lilly and company (Indianapolis, USA) and used as a working standard. Axid capsules (150 and 300 mg of nizatidine) were supplied from Eli Lilly. Bromothymol blue (BTB), bromocresol green (BCG) and dichloromethane were manufactured by Aldrich. All chemicals were of analytical grade and manufactured by Merck and BDH. Water was doubly-distilled and stored in a glass container.

Solutions

A freshly prepared 5.0×10^{-3} M aqueous solution of pure nizatidine was used as stock solution. BCG and BTB solutions (1.0×10^{-3} M) were prepared by dissolving the appropriate amounts in about 2 mL of 0.1 M sodium hydroxide, then 20 mL of ethanol (96%) were added and the volume was completed to exactly 100 mL using double distilled water. Citrate buffers were prepared as described by Heyrovsky and Zuman [14].

Voltammetric Procedure

The general procedure for obtaining differential pulse adsorptive stripping voltammogram was as follows: 9.0 mL of citrate buffer solution (pH 3.2) was placed in the voltammetric cell and deaerated with highly pure nitrogen for 8 min with stirring. A preconcentration (accumulation) potential of -0.20 V was applied to a fresh mercury drop, usually for 20 s, while the solution was stirred. The stirrer was switched off to let the solution be quiescent in the last 15 s. A negative potential scanning was initiated between 0.0 to -0.6 V using the differential – pulse mode. The operational parameters of the scan were scan rate 10 mVs^{-1} and pulse amplitude 50 mV. After background stripping voltammograms had been obtained, the adsorptive stripping was repeated with a new mercury drop after the addition of an appropriate volume of solution containing a concentration of NIZ in the range $3.0 \times 10^{-8} - 1.0 \times 10^{-6}$ M. After each sample addition, a deaeration for about 2 min was made.

Spectrophotometric Procedure

Into a 100-mL separatory funnel transfer exactly 5.0 mL of 9.0×10^{-4} M BCG or 2.0 mL of 9.0×10^{-4} M BTB, followed by 5.0 mL of citrate buffer of the recommended pH and an appropriate volume of solution containing an amount of NIZ in the range 3.0–90 µg, in that order and the volume is completed to 12 mL with water. Extract the aqueous solution with two separate 10-mL portion of dichloromethane, shaking well to ensure complete extraction (about 1 min). Dilute combined dichloromethane extracts to exactly 25.0 mL with dichloromethane and determine the absorbance in a tightly stoppered cell at 416 nm against a reagent blank prepared similarly without the addition of NIZ, in a thermostated bath at a temperature in the range 20–30 °C.

Analysis of Tablets

The NIZ drug was commercially available as Axid (Eli Lilly, USA) and is claimed to contain 150 or 300 mg per tablet. Ten tablets of each drug were weighed accurately and finely powdered. An

accurately weighed amount of powder (equivalent to 1/10 tablet average weight) was transferred quantitatively into a 250-mL calibrated flask, diluted to volume with doubly distilled water and the mixture was shaken well for 30 min. An appropriate volume of supernatant solution was used for voltammetric and spectrophotometric determination of NIZ under the optimum experimental conditions. The concentration of NIZ was determined from the previously plotted calibration curves.

Results and Discussion

Voltammetric Measurements

NIZ was found to be electrochemically active and exhibits a cathodic stripping peak at −0.30 V after accumulation at −0.20 V in citrate buffer solution (pH 3.2) at a hanging mercury drop electrode (HMDE). Systematic studies of various experimental parameters that affect the differential-pulse adsorptive cathodic stripping voltammetric (DP-AdCSV) response were carried out in order to optimize the experimental conditions for the determination of NIZ.

Effect of pH

The effect of pH on the DP-AdCSV peak current and potential of 5.0×10^{-6} M NIZ was studied over the pH range 2.6–10.5, the obtained results are presented in Fig. 1 and Table 1. NIZ molecule exhibits one or two reduction peaks depending on the pH of supporting electrolyte. It was found that at pH 2.6 one reduction peak was obtained and its height was found to increase gradually by increasing the pH up to pH 3.2. Any further increase in the pH affected a gradual decrease in the peak height until it disappeared at pH above 9.5. A second peak was developed at pH higher than 4.2 and its height was found to increase gradually by increasing the pH until it reached its maximum height at pH 9.5, beyond which any further increase in the pH did not affect the peak height. On the other hand, in all studied buffer solutions, a third reduction peak has been observed at more negative potential overlapping with a hydrogen reduction peak. This peak is an adsorptive catalytic peak where the catalytic activity of structurally similar compounds (e.g. ranitidine [15, 16] and famotidine [17, 18]) has been reported. Squella et al. [18] found that the famotidine drug, which can not be electrochemically reduced at the DME, exhibits a catalytic proton reduction wave.

Table 1. Effect of pH on the height and potential of DP-AdCSV peak of 1.0×10^{-6} M NIZ in citrate buffer solutions, other conditions as in Fig. 1

pH	Peak potential, −E(V)		Peak current, μA	
	First peak	Second peak	First peak	Second peak
2.6	0.27	–	0.25	–
3.2	0.30	–	0.50	–
4.2	0.40	0.83	0.37	0.18
5.2	0.47	0.90	0.11	0.45
6.2	0.52	1.00	0.10	0.52
7.5	0.62	1.05	0.10	0.63

The peak response was examined in the presence of different buffer solutions, e.g., acetate, citrate and Britton-Robinson buffers. Citrate buffer was selected as the most suitable since it gave the highest response and good repeatability, as shown in Table 2. On the other hand, it was found that the presence of peaks is strongly influenced by pH and the buffer constituents. These results are in good agreement with those obtained by Kapetanovic et al. [9].

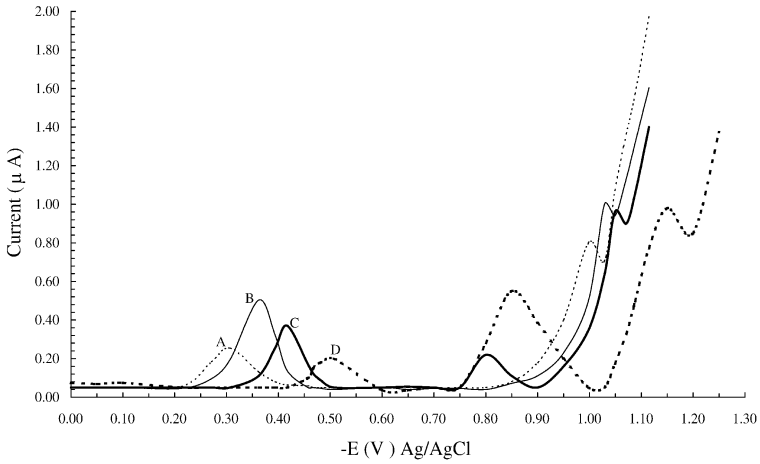

Fig. 1. Differential – pulse adsorptive cathodic stripping (DP-AdCSV) voltammograms for 1.0×10^{-6} M NIZ; (*A*) pH 2.6; (*B*) pH 3.2; (*C*) pH 4.2 and (*D*) pH 5.2. Accumulation potential −0.20 V; accumulation time 20 s; pulse amplitude 50 mV and scan rate 10 mVs^{-1}

Table 2. Effect of buffer constituents on the DP-AdCSV peak of 1.0×10^{-6} M NIZ at pH 3.2. Other conditions as in Fig. 1.

Buffer (pH 3.2)	Peak Current (μA)	Peak potential −E(V)	Peak half-width $W^{1/2}$(mV)
Acetate	0.32	0.25	120
Britton-Robinson	0.35	0.38	112
Citrate	0.50	0.30	108

The reduction mechanism of some drugs containing NO_2 group was previously reported. The reduction mechanism takes place in a similar way as that reported by Zamareno et al. [16] and Abu Zuhri et al. [15] for the reduction of ranitidine, which have a similar structure as nizatidine.

The cyclic voltammetric behavior of 5.0×10^{-6} M NIZ in citrate buffer (pH 3.2) exhibits only a cathodic peak with no peaks in the anodic scan, indicating the irreversibility of the reduction process. The cathodic peak height was directly proportional to the scan rate and the peak potential shifts linearly to more negative potential when the scan rate is increased, indicating the reduction of the adsorbed species [19]. As shown in Fig. 1, the reduction peak in citrate buffer (pH 3.2) is relatively high, sharp and reproducible. Therefore pH 3.2 was selected as optimum pH for analytical purposes.

Effect of Accumulation Time

DP-AdCSV peak heights of 7.0×10^{-7} M NIZ after different accumulation times and a plot of the resulting current versus accumulation time has been shown in Fig. 2. At first, the current increases linearly with time and then starts to level off. The deviation from linearity occurs after accumulation time of 20s.

Effect of Accumulation Potential

The effect of accumulation potential on the peak current was studied over the potential range 0.0 to −0.4 V. The highest peak current was observed for an accumulation potential at −0.20 V. A gradual decrease in the peak height was observed on changing the potential to more negative or less negative potentials than −0.20 V. Therefore, an accumulation potential of −0.20 V offered the best signal-to-background characteristics and was used in all subsequent work.

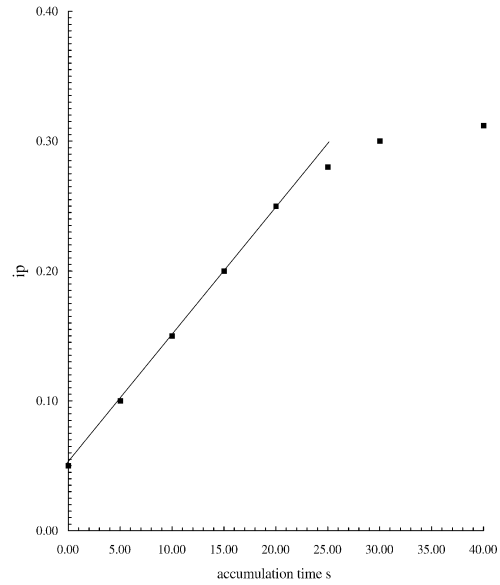

Fig. 2. Current-accumulation time plots for 7.0×10^{-7} M NIZ. Other conditions as in Fig. 1

Effect of Other Parameters

Several instrumental parameters, e.g. scan rate, pulse amplitude, rest period and drop size were optimized. The chosen conditions for NIZ determination were $10\,mVs^{-1}$, 50 mV, 15 s and small drop size, respectively. Higher pulse amplitudes enhance peak currents but are not preferred as the peak potentials get further away from $E_{1/2}$ in classical DC polarography.

Effect of Excipients

The effect of the presence of some common excipients normally used in NIZ formulations on the response of 5.0×10^{-6} M NIZ determined according to the recommended procedure were evaluated. The results obtained are summarized in Table 3. It was found that there is no significant interference from these excipients if they are present in 50-fold mass excess.

Calibration Curves for Voltammetric Determination of NIZ

The applicability of DP-AdCSV technique as an analytical method for determination of NIZ was tested. The recommended conditions for DP-AdCSV determination of NIZ were as follows: citrate buffer (pH 3.2), accumulation time 20s, accumulation potential −0.20 V, pulse amplitude 50 mV and scan rate $10\,mVs^{-1}$. Under the aforementioned recommended

Table 3. Effect of excipients on the voltammetric determination of 1.0×10^{-6} M NIZ at the recommended conditions

Excipient	NIZ: excipient (mass ratio)	% Recovery
Sucrose	1:1	99.98
	1:20	99.90
	1:50	98.20
	1:100	97.90
Talc powder	1:1	99.95
	1:20	99.30
	1:50	98.90
	1:100	98.50
Magnesium stearate	1:1	99.95
	1:20	99.00
	1:50	97.50
	1:100	96.90
Starch	1:1	99.90
	1:20	98.80
	1:50	96.90
	1:100	96.00
Arabic gum	1:1	99.90
	1:20	99.40
	1:50	98.20
	1:100	97.20

conditions, the height of the DP-AdCSV peak increases gradually with increasing the concentration of NIZ. A linear calibration graph from 3.0×10^{-8} to 1.0×10^{-6} M NIZ was obtained after a 20s accumulation time at -0.20 V accumulation potential. The straight line has a slope of $3.50 \times 10^{5}\ \mu A M^{-1}$ and the regression line equation was found to be $Y(\mu A) = 0.0015 + 3.50 \times 10^{5} X(M)$. The validity of the method is supported by the constancy of the i_p/C. The detection limit was found to be 3.0×10^{-8} M (the detection limit could be lowered to 1.0×10^{-8} M after 180s accumulation time at -0.2 V accumulation potential). The relative standard deviation was in the range 1.2–2.0% for six measurements. The repeatability of the method was checked by measurements on six 1.0×10^{-7} M, 5.0×10^{-7} M and 8.0×10^{-7} M NIZ solutions. The relative standard deviation was in the range 1.2–2.0%, with a recovery in the range 97.0% 100.6%.

Application of DP-AdCSV Method to Analysis of Formulations

The validity of the DP-AdCSV method for the determination of NIZ in pharmaceutical preparations was investigated by assaying Axid (labeled to contain either 150 mg or 300 mg per tablet of NIZ). Ten analyses of five different samples of each drug gave a mean recovery of 99.6% and 100.8% for the 150 and 300 mg drugs, respectively.

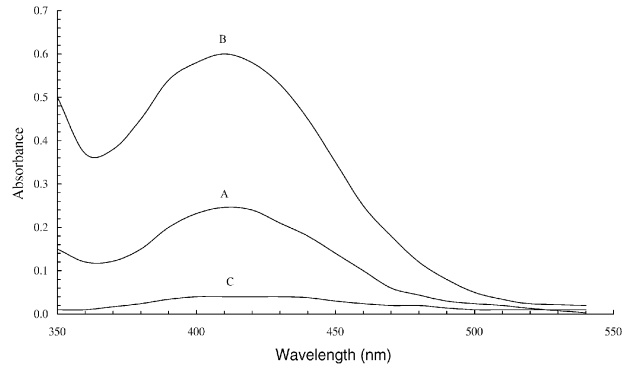

Fig. 3. Absorption spectra of (A) a mixture containing 8.0×10^{-5} M NIZ and 4.0×10^{-4} M BCG at pH 4.0 against reagent blank. (B) a mixture containing 1.1×10^{-4} M NIZ and 2.0×10^{-4} M BTB at pH 6.2 against reagent blank. (C) reagent blank (containing BCG or BTB) against dichloromethane, temperature = 25 °C

Spectrophotometric Measurements

Absorption Spectra

Figure 3 shows the absorption spectra of the yellow products formed between NIZ and each of BTB and BCG in dichloromethane. The obtained spectra exhibit an absorption peak at 416 nm. The colored product is most probably due to the formation of either NIZ-BTB or NIZ-BCG ion-pair complexes. Neither NIZ nor BTB and BCG alone display any significant absorption in dichloromethane at 416 nm as shown in the Fig. 3.

Effect of Organic Solvent on Extraction

Many organic solvents were examined in order to find the most suitable one for the extraction of NIZ-BCG and NIZ-BTB ion-pair complexes. Among the examined organic solvents were chloroform, n-hexane, toluene, benzene, dichloromethane, carbon tetrachloride and nitrobenzene. In the proposed methods, dichloromethane was found to be the most suitable for both ion-pair complexes, since it gave the highest percent of extraction of NIZ and the color of the organic phase was stable for at least 48 hours.

Effect of pH on Absorbance

The effect of pH on the absorbance of the organic phase (dichloromethane) was studied in the pH range

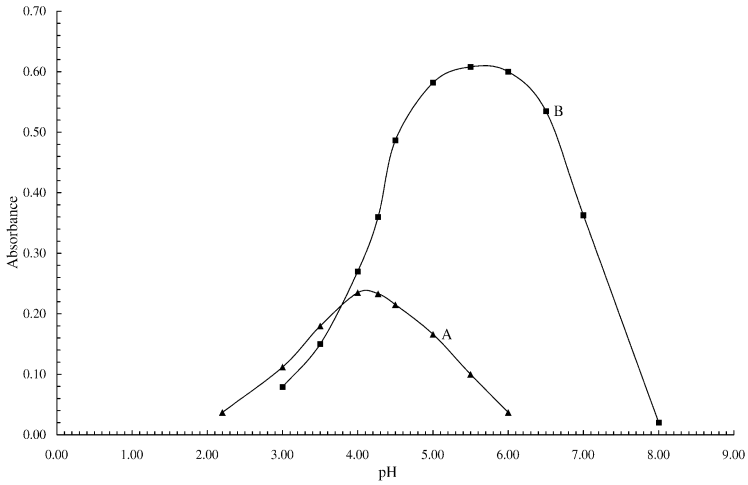

Fig. 4. Effect of pH on absorbance of (*A*) NIZ-BCG, (*B*) NIZ-BTB. Conditions: [NIZ]= 8.0×10^{-5} M, [BCG]= 4.0×10^{-4} M, [BTB]= 1.5×10^{-4} M, $\lambda =$ 416 nm, temperature = 25 °C

2.2–8.0 for both ion-pair complexes under investigation. The solutions were prepared as described in the general procedure and the obtained results are presented in Fig. 4. It was found that for NIZ-BCG and NIZ-BTB ion-pair complexes increasing the pH affected a gradual increase in the absorbance up to pH 4.0 and 6.0, respectively. Beyond these pH values any further increase in the pH affected a gradual decrease in the absorbance.

Effect of Reagent Concentration

The effect of the concentration of BCG and BTB on the absorbance of the organic phase was studied for solutions containing a fixed amount of NIZ and prepared as described in the general procedure. It was found that increasing the concentration of either BCG or BTB affected a gradual increase in the absorbance up to a concentration of 1.8×10^{-4} M in case of BCG and 0.7×10^{-4} M in case of BTB. Any further increase in the dye concentration did not show any increase in the absorbance but it affected formation of an emulsion and subsequently, longer time for the two phases to separate was required. In the present work 5.0 mL of 9.0×10^{-4} M solution of BCG or 2.0 mL of 9.0×10^{-4} M solution of BTB were found to be sufficient for the production of maximum and reproducible color intensity.

Effect of Number of Extraction Times on Absorbance

The effect of number of extractions on the extraction efficiency was studied for both ion-pair complexes. The solutions were prepared as described in the general procedure but different number of extractions was examined. In the present work it was found that two

Table 4. The optimum conditions and analytical characteristics for spectrophotometric determination of NIZ using BCG and BTB

Parameter	NIZ-BCG method	NIZ-BTB method
λmax (nm)	416	416
Recommended pH	4.0	6.2
Shaking time (s)	60	20
Reagent concentration (M)	1.8×10^{-4}	0.7×10^{-4}
Recommended temperature range(°C)	20–30	20–30
Range of linearity (M)	$6.0 \times 10^{-7} - 1.8 \times 10^{-5}$	$3.0 \times 10^{-7} - 1.1 \times 10^{-5}$
Correlation coefficient	0.9997	0.9983
Molar absorptivity ($\mathrm{l.mol^{-1}cm^{-1}}$)	2.1×10^4	3.2×10^4
Detection limit (M)	6.0×10^{-7}	3.0×10^{-7}
Range of relative standard deviation (%)*	1.2–4.7	2.1–6.0
Beer's law equation	$Y = 0.009 + 2.1 \times 10^4\,(M)$	$Y = 0.003 + 3.2 \times 10^4\,(M)$

* Average of six measurements.

Table 5. Comparison between different methods used for determination of NIZ in raw material

Method	Medium	Detection limit (M)	Linear range (M)	Recovery (%)	r.s.d (%)	Ref.
Spectrophotometry	BR-buffer (pH 3.5)		$1.0 \times 10^{-6} - 9.0 \times 10^{-5}$	99.3–102	1.27–3.28	5
Extractional spectrophotometry	citrate buffer pH 3.25	2.5×10^{-5}	$2.5 \times 10^{-5} - 3.5 \times 10^{-4}$	98.85	0.68–1.48	6
HPLC	pH 9.5 ($CHCl_3$-propanol)	5.4×10^{-8}	$1.5 \times 10^{-7} - 1.5 \times 10^{-5}$		11.2	2
Spectrophotometric using BCG	citrate buffer pH 4.0/CH_2Cl_2	6.0×10^{-7}	$6.0 \times 10^{-7} - 1.8 \times 10^{-5}$	99–100.2	1.2–4.7	present work
Spectrophotometric using BTB	citrate buffer pH 6.2/CH_2Cl_2	3.0×10^{-7}	$3.0 \times 10^{-7} - 1.1 \times 10^{-5}$	-	2.1–6.0	present work
Voltammetry	citrate buffer pH 3.2	3.0×10^{-8}	$3.0 \times 10^{-8} - 1.0 \times 10^{-6}$	99.6–100.8	1.2–2.0	present work

successive extractions with 10-mL portions of dichloromethane were sufficient to give complete extraction of either NIZ-BCG or NIZ-BTB ion-pair complexes.

Effect of Shaking Time

The effect of shaking time of the two phases on the extraction efficiency was studied for both ion-pair complexes. In the present work 60s shaking time in case of NIZ-BCG and 20s shaking time in case of NIZ-BTB were found to be sufficient for complete extraction when two successive extractions with 10-mL portions of dichloromethane were used.

Effect of Temperature

The effect of temperature after extraction on the absorbance of the organic phase was studied for both ion-pair complexes in the temperature range 20–30 °C. No detectable change in the absorbance was found. However, higher temperature could affect an increase in the absorbance due to the evaporation of dichloromethane. In the present work all measurements were carried out in a thermostated bath at 25 °C.

Effect of Time

The effect of time after separation of the organic phase on the absorbance was studied for both systems. The obtained results showed that maximum color intensity was attained after 30s of separation of the organic phase and the intensity remained constant for at least 48 hours.

Stoichiometry of the Ion-Pair Complex

The stoichiometry of the ion-pairs formed between NIZ and BCG or BTB was investigated at the recommended conditions for each dye by applying the molar ratio and continuous variation methods. The results indicated the existence of 1:1 ion-pairs in all cases.

Interference Studies

Interference by foreign species was studied for the determination of 1.0×10^{-5} M NIZ using both NIZ-BCG and NIZ-BTB ion-pair complexes. Since the aim of the present work is to determine NIZ in pharmaceutical formulations, the effect of the com-

mon excipients was specially considered. The obtained results showed that glucose, starch, sucrose, arabic gum, talc powder and magnesium stearate had no effect on the accuracy of the results when the additive to NIZ mass ratio did not exceed 50:1.

Analytical Applications

Under the described recommended conditions, standard calibration curves for NIZ with BCG and BTB were constructed by plotting absorbance versus concentration. Beer's law was valid over NIZ concentration ranges $6.0 \times 10^{-7} - 1.8 \times 10^{-5}$ M and $3.0 \times 10^{-7} - 1.1 \times 10^{-5}$ M for BCG and BTB, respectively. The regression line equations were derived to be $Y = 0.009 + 2.1 \times 10^4 X(M)$ and $Y = 0.003 + 3.0 \times 10^4 X(M)$ for BCG and BTB, respectively. Table 4 summarizes the optimum conditions for determination of NIZ as well as the spectral characteristics of the ion-pairs.

Six replicate determinations at different concentration levels were carried out for pure raw material to test the precision of the method. The relative standard deviations were found to be in the range 2.1–6.0% and 1.2–4.7% for BCG and BTB methods, respectively. Table 5 summarizes the results obtained for the determination of NIZ using the suggested voltammetric and spectrophotometric methods as well as other reported methods.

Spectrophotometric Analysis of Pharmaceutical Formulations

The validity of the proposed spectrophotometric method for determination of NIZ using BCG reagent was checked by determining NIZ in axid tables (150 and 300 mg NIZ per tablet). Recovery in the range 99.6–100.2% was obtained.

Conclusion

The proposed voltammetric method, based on the adsorptive cathodic stripping analysis at HMDE could be successfully used for determining NIZ as raw material and in pharmaceutical formulations. The method was proved to be sensitive, accurate and precise (rsd = 1.2–2.0%) with a linear range of $3.0 \times 10^{-8} - 1.0 \times 10^{-6}$ M NIZ. The advantage of the voltammetric method lies in its lower detection limit (3.0×10^{-8} M), economy of time and reagents. On the other hand, excipients in the dosage forms do not interfere in the analysis. These advantages make the voltammetric method suitable for routine quantification of NIZ in pharmaceutical preparations, whereby there is no official method for the determination of nizatidine as a drug listed in the pharmacopoeias.

Comparison between different methods for determination of NIZ (Table 5) indicates that the proposed voltammetric method is the most sensitive with the lowest detection limit. The proposed two spectrophotometric methods using BCG and BTB can be used as alternative methods for spectrophotometric determination of NIZ with reasonable sensitivity, selectivity and accuracy.

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