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Spectrophotometric studies using ion-pair formations of Ranitidine hydrochloride in pure and in Pharmaceutical forms with some dyestuff reagents

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ABSTRACT

Simple, rapid and sensitive spectrophotometric procedure is suggested for the determination of ranitidine hydrochloride (RNH) drug in pure form and in pharmaceutical formulations. The method was based on the ion-pair formations of RNH with different dyestuff reagents such as methyl orange (MO), bromocrysol purple (BCP), eriochrome cyanine R (ECR) and alizaraine red S (ARS). The obtained ion-pairs were measured spectrophotometrically at 408, 420, 330 and 326 nm by using BCP, MO, ECR and ARS reagents, respectively. Beer's plots were linear in the concentration range of 5-200, 20-350, 10-150 and 10-180 µg mL^{-1} RNH, with correlation coefficients not less than 0.9991, 0.9996, 0.9993 and 0.999 using BCP, MO, ECR and ARS reagents, respectively. The Sandell sensitivity was found to be 0.813, 0.462, 0.541and 0.630 µg cm^{-2} for BCP, MO, ECR and ARS, respectively. Standard deviation (SD = 0.024-0.028, 0.018-0.023, 0.016-0.021 and 0.023–0.029) and relative standard deviation (RSD% = 0.123-0.943, 0.0102-0.82, 0.118-0.145 and 0.132-0.178%) (n = 4) values using BCP, MO, ECR and ARS reagents, respectively, were obtained. These results were also confirmed with percent recovery of 99.78–100.52%, 99.86-101.12%, 99.82–100.31% and 100.18-101.25 % for BCP, MO, ECR and ARS reagents, respectively. This method was successfully applied for determination of RNH in aciloc tablet. The calculated t- and F- values (95% confidence limit) indicate no significant differences between the proposed and official methods.

INTRODUCTION

Ranitidine hydrochloride (RNH), chemically N, N dimethyl-5- (2-(1-methylamine- 2 -nitrovinyl) -ethylthiomethyl) furfurylamine hydrochloride. It is a H2-receptor antagonist and is widely used in short term treatment of duodenal ulcer and in the management of hypersecretory conditions (Remington 1985). It acts by blocking histamine receptors which are present on the cells in the stomach lining.

Ranitidine binds to H2 receptors, replacing some of the histamine. As a result, the amount of stomach acid produced by these cells is decreased. Ranitidine decreases the amount of acid in the stomach and duodenum. Ranitidine helps relieve the symptoms of indigestion and aids the healing of ulcers. It is also used to depress acid production in various other conditions.

The molecular formula is $C_{13}H_{22}N_4O_3S{\cdot}HCl$, representing a molecular weight of 350.87 g mol^{-1}. It is a white to pale yellow, crystalline substance that is soluble in water.

Several methods have been reported for the determination of ranitidine in bulk, pharmaceutical dosage forms, and/or biological fluids.

These methods include kinetic spectrophotometry (Hassan and Belal 2002, Walash et al 2002), HPLC (Rustum 1988-Campanero et al 1998), coulometry (Nikolic et al 1995), capillary electrophoresis (Kelly et al 1996, Shou-Mei et al 2001), fluorimetry (Lopez et al 1996), HPTLC (Khadiga et al 2002), voltammetry (Parviz et al 2007), potentiometry (Hunag et al 2000 – Frag et al 2011) and polarography (Richter et al 1999).

But, such techniques are time consuming because of extensive sample pretreatment, require expensive instrumentation and beyond the reach of small laboratories, particularly in under developed and developing countries.

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There are several reports for the determination of RNH by spectrophotometry involving the use of Folin-Ciocalteu reagent (Basavaiah and Nage 2004), N-bromosuccinimide (Sastry et al 1997), Cerium (IV) (Amin et al 2003), 3-methyl-2-benzothiazoline hydrazone-iron (III) (Rao et al 1987), 7, 7, 8, 8 tetracyanoquinodimethane (Al-Ghannam and Belal 2002), 2, 6-dichloroquinone chlorimide (Emmanuel and Haldankar 1989), bromothymol blue (Ozsoy and Guvner 1987), potassium dichromate (Basavaiah and Somashekar 2007), perchloric acid (Basavaiah et al 2005), 2,3-dichloro-5,6-dicyano-p-benzoquinone (DDQ) (Walash et al 2004), $Hg(SCN)_2$ (Basavaiah and Somashekar 2007) and p-dimethylaminobenzaldehyde (PDAB) (Badiadka et al 2010).

The aim of this work is to find a fast, accurate and simple spectrophotometric method for the assay of RNH in pure form and in some available pharmaceuticals in the Egyptian markets. The method depends on the ion-pair formations of RNH with methyl orange (MO), bromocrysol purple (BCP), eriochrome cyanine R (ECR) and alizaraine red S (ARS) as dyestuff reagents. The different experimental conditions, stoichiometry and mechanism of the reactions were studied. The MO, BCP, ECR and ARS reagents are used to determine RNH drug in pure form and in aciloc tablet. Different parameters are optimized in order to validate the method to be applied for routine measurement of RNH.

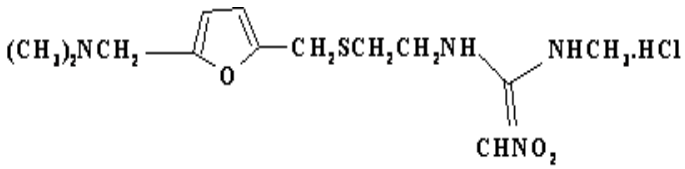

Fig. 1: Structural formula of RNH drug.

Experimental

Materials

All chemicals and reagents used were of analytical reagent grade and some of them were used as such without any further purification. They included ranitidine hydrochloride (RNH) provided by GlaxosmithKline Egypt. Reagents used included methyl orange (MO), bromocrysol purple (BCP), eriochrome cyanine R (ECR) and alizaraine red S (ARS) were purchased from win lab, U.K.

Sodium hydroxide was supplied from Adwic and hydrochloric acid was supplied from Merck. Chloroform, ethylene chloride and methylene chloride were supplied from El-Nasr Company. Ranitidine hydrochloride pharmaceutical preparation (Aciloc tablet, 75 mg/tablet) was purchased from Sedico Company, Egypt.

Apparatus

The spectrophotometric measurements were carried out using the manual Unico 1200 (United Products and Instruments, Inc.) ranged from 325-1000 nm. Adjustment of pH was done using HANNA, model ZH, Romania.

General procedures

Aliquot volumes of standard stock solution, containing 1 mg mL^{-1} RNH was transferred to 10 mL calibrated flasks. 1 mL of the reagent was added and diluted to volume with bi-distilled.The absorbances of the resulting solutions were measured at the wavelength of maximum absorption (408, 420, 330 and 326 nm by using BCP, MO, ECR and ARS, respectively) after the appropriate times, at 25±2 ºC against reagent blanks treated similarly.

Procedure for the assay of the tablets

Three tablets were weighed and an accurately weighed amount of the finely powdered tablets equivalent to 100 mg of RNH was transferred into a 100 mL beaker and dissolved in bi-distilled water. The volume was made up to 100 mL with bi-distilled, the solution was filtered and the procedure was continued as mentioned under general procedure. The concentration of RNH drug in the tablet was determined from the calibration graph.

Stoichiometric relationship

In Job's method of continuous variation (Jop 1928), a series of solutions were prepared by mixed equimolar of RNH drug and reagent in varying portions, which keeps the total concentration constant at (3.7×10^{-4} mol L^{-1}) in case of BCP, at (6.11×10^{-4} mol L^{-1}) in case of MO, at (3.73×10^{-4} mol L^{-1}) in case of ECR or at (5.84×10^{-4} mol L^{-1}) in case of ARS.

The procedure was followed as above and the absorbance data obtained were plotted against mole fraction of drug for each indicator. Two straight lines were obtained which intersect at the reactants ratio. In the molar ratio method (Vosburgh and Cooper 1941), a series of solutions were prepared in which drug solution of RNH was kept constant at 3.7×10^{-4}, 6.11×10^{-4}, 3.73×10^{-4} and 5.84×10^{-4} mol L^{-1} in case of BCP, MO, ECR and ARS respectively, while that of BCP solution was regularly varied from 0.25 to 4 ml of 3.7×10^{-4} mol L^{-1}, MO solution was regularly varied from 0.25 to 3 ml of 6.11×10^{-4} mol L^{-1}, ECR solution was regularly varied from 0.1 to 1.6 ml of 3.73×10^{-4} mol L^{-1} and ARS solution was regularly varied from 0.25 to 3 ml of 5.84×10^{-4} mol L^{-1}.The final volume was completed to 10 mL bi-distilled water using volumetric flask and the absorbance was measured against ratio of reactants.

RESULTS AND DISCUSSION

Absorbtion spectra

The absorption spectra of the extracted ion-pairs in chlorofprm are scanned against blank reagent in the wavelength range from 320 to 520 nm and the results obtained are represented graphically in Figure (2). This figure shows that the ion-pairs attain their maxima at 408, 420, 330 and 326 nm using BCP, MO, ECR and ARS reagents, respectively.

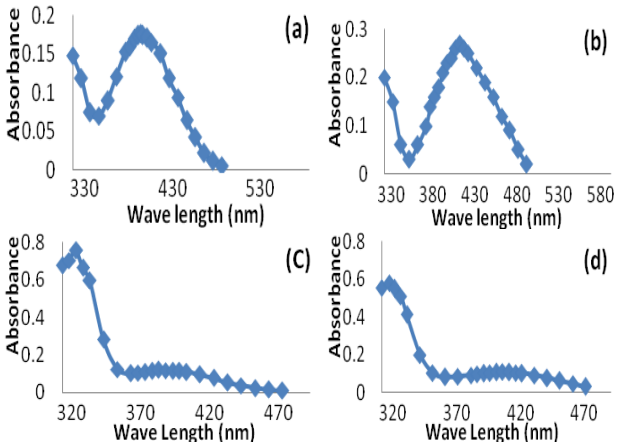

Fig. 2: Absorption spectra of RNH ion pairs with (a) BCP, (b) MO, (c) ECR and (d) ARS reagents.

Optimization of variables

The influence of some variables on the reaction has been tested as follows.

Effect of solvent

The effect of using different types of solvents for the extraction of the formed ion pairs and subsequently determination of this drug are studied. The results indicate that, acetone, methanol, ethanol, tetrahydrofuran and 1,4-dioxane cannot be used for the extraction of the ion-pairs formed where they are miscible with the reaction mixture, while dichloroethane, methylene chloride and chloroform can be used for its quantitative extraction. Table (1) shows the obtained absorbance and the respective molar absorptivity values of the ion-pairs using different extractive solvents. It is obvious from this table that methylene chloride is the suitable solvent for extraction in case of BCP and ARS reagents, while chloroform is used in case of MO and ECR reagents.

Effect of reagent concentration.

In this experiment, the RNH concentration is kept constant at 1mg/mL, while the concentration of BCP, MO, ECR and ARS reagents are varied from 20–1600 µg mL^{-1}. Figure (3) shows the effect of varying BCP, MO, ECR or ARS concentrations on the spectra of the ion-pairs formation between reagents and RNH drug. This figure shows that, the absorbance of the extracted ion-pairs increased by increasing the concentrations till 1000, 800, 400 and 500 µg mL^{-1} using BCP, MO, ECR and ARS reagents, respectively. Above these values, the absorbance slightly decreased even with further addition of the reagents. So any excess of reagents have no effect on the determination of the RNH drug.

Effect of time and temperature

The effect of time on the formation of the ion pairs is studied carefully and the results obtained are illustrated in Figure (4). The optimum time for the completion of the reaction was 15, 10, 5 and 5 minutes using BCP, MO, ECR and ARS reagents, respectively. The absorbance values remain almost unchanged with the increase of time. The intensity of the colour formed after extraction by chloroform is stable for at least 24 hours. The absorbance temperature curve of the reaction of RNH drug with BCP, MO, ECR or ARS reagents is constructed at specified λ_{max} for the drug with each reagent, and the results obtained are represented graphically in figure (5). The absorbance of the extracted ion-pairs is measured in the temperature range from 0 to 60 ºC. It is clear from the curve that, the absorbance is generally increased with the increase of temperature and attains maximum value at 30, 28, 20 and 26 ºC for RNH drug with BCP, MO, ECR and ARS reagents, respectively. The absorbance is slightly decreased above this temperature. Therefore, the temperatures chosen are 30, 28, 20 and 26 ºC as the best temperature for determination of the drug under study in pure and pharmaceutical formulation.

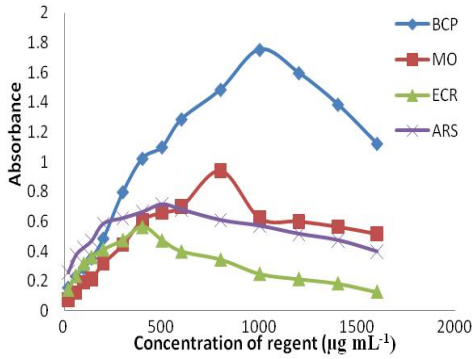

Fig. 3: Effect of BCP, MO, ECR or ARS concentration on the spectra of RNH- reagent ion- pairs

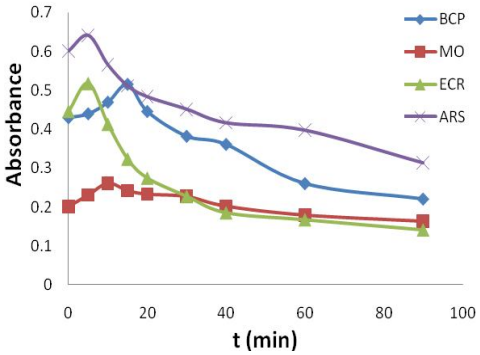

Fig. 4: Effect of time on the spectra of the RNH ion pairs with BCP, MO, ECR and ARS reagents.

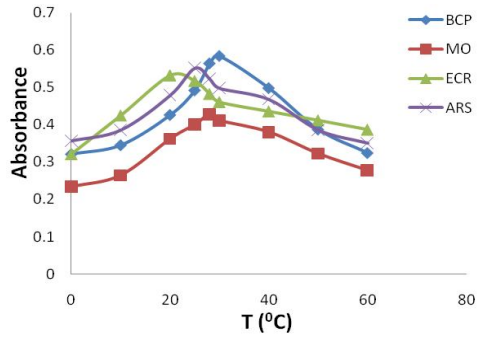

Fig. 5: Effect of temperature on the spectra of the RNH ion pairs with BCP, MO, ECR and ARS reagents.

Stoichiometric ratio (Composition of CT-complexes)

Job's method of continuousvariation (Jop 1928) and molar ratio (Vosburgh and Cooper 1941) methods were used for determining the molar ratios of the investigated drug and reagents (BCP, MO, ECR and ARS) to select the optimum conditions for its micro determination (Figures6 and 7). The results show that, 1:1 ion-pairs are formed with the investigated drug using BCP, MO, ECR or ARS reagents.

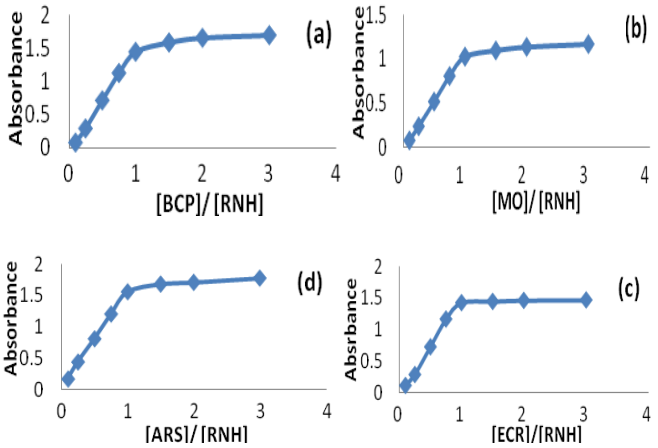

Fig. 6: Stiochiometric ratio of the reaction of RNH with (a) BCP, (b) MO, (c) ECR and (d) ARS reagents using molar ratio method.

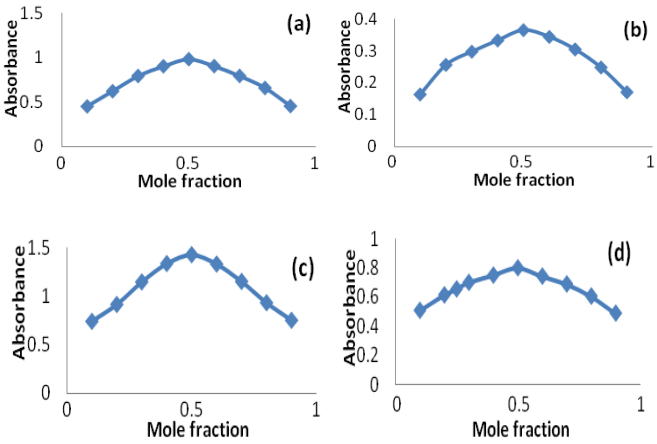

Fig. 7: Stiochiometric ratio of the reaction of RNH with (a) BCP, (b) MO, (c) ECR and (d) ARS reagents using the continues variation method (Job's method).

Obeyence of Beer's law

Spectrophotometric determination of RNH drug is carried out under favourable conditions of suitable wavelength, extracting solvent, reagent concentration, reaction time, temperature, and ratios. The results of determination of the drug under investigation are shown in Table (2).

The validity of Beer's law for the formed ion-pairs through the reaction of the drug under study with BCP, MO, ECR and ARS reagents is shown in Figure (8).

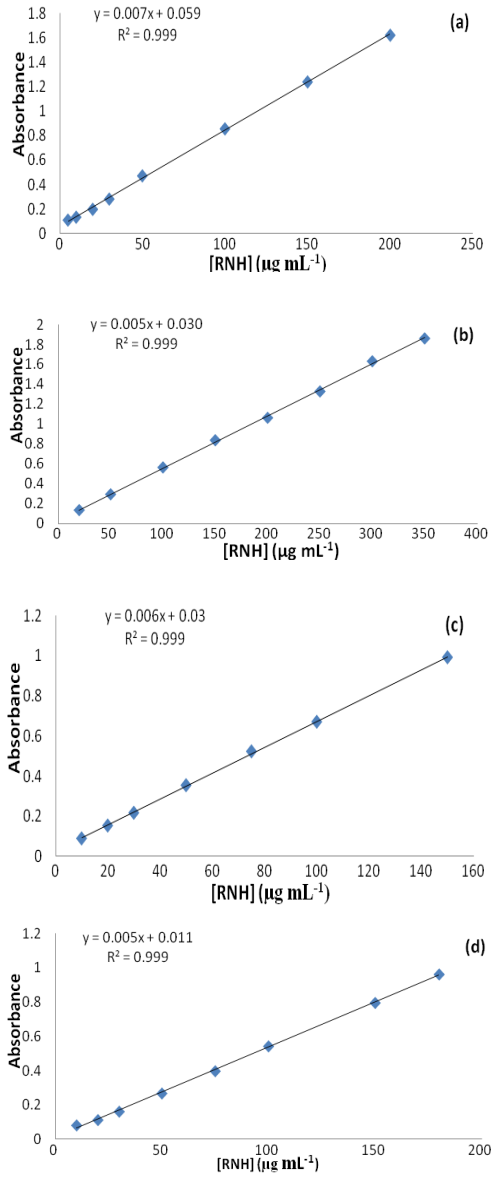

Fig.8: Beer's law plots for the determination of RNH drug using (a) BCP, (b) MO, (c) ECR and (d) ARS reagents.

Analysis of pharmaceutical formulations

The validity of the proposed method is examined for the determination of RNH drug in dosage form manufactured in the local companies. The concentration of the drug in the dosage form is calculated from the appropriate calibration graph. There is no shift in the absorption maximum due to the presence of other constituents of the dosage form. The determination of RNH drug in the dosage form is compared with those obtained by applying the official method (Ruiz et al 2001) (Table 3). The results obtained are compared statically by the percent recovery, t-test and F-test with those obtained by the official method on samples of the same batches. The values did not exceed the theoretical tabulated values indicating that there is no significant difference between accuracy of the proposed and official method.

Table. 1: The absorbance and molar absoptivity (ε) values for the determination of RNH drug using BCP, MO, ECR and ARS reagents in different solvents.

Solvent	Absorbance (A)				ε (L mol^{-1} cm^{-1})			
	BCP	MO	ECR	ARS	BCP	MO	ECR	ARS
Chloroform	0.376	0.396	0.582	0.490	1.32 x10^3	1.39 x10^3	2.04 x10^3	1.72 x10^3
Ethylene chloride	0.229	0.119	0.330	0.380	8.04 x10^2	4.18 x10^2	1.16 x10^3	1.33 x10^3
Methylene chloride	0.534	0.285	0.266	0.522	1.87 x10^3	1.00 x10^3	9.33 x10^2	1.83 x10^3

Table. 2: Analytical parameters for the determination of RNH drug using BCP, MO, ECR and ARS reagents.

Reagent Parameters		BCP	MO	ECR	ARS
λ_{max} (nm)		408	420	330	326
time (min)		15	10	5	5
T (^{0}C)		30	28	20	26
(RNH) (µg mL^{-1})		5-200	20-350	10-150	10-180
ε (L mol^{-1} cm^{-1})		1.78 x10^3	1.65 x10^3	3.43 x10^3	1.73 x10^3
(S) (µg cm^{-2})		0.813	0.462	0.541	0.630
(%) Recovery		99.78-100.52	99.86-101.12	99.82-100.31	100.18-101.25
A = mC +Z	m	0.007	0.005	0.006	0.005
	Z	0.059	0.030	0.030	0.011
R		0.9991	0.9996	0.9993	0.999
SD		0.024 - 0.028	0.018 - 0.023	0.016-0.021	0.023-0.029
RSD (%)		0.123 - 0.943 %	0.102- 0.82 %	0.118-0.145 %	0.132-0.178 %
LOD (µg mL^{-1})		3.182	16.384	8.233	9.294
LOQ (µg mL^{-1})		10.606	54.608	27.441	30.977

Table. 3: Spectrophotometric determination of RNH drug in pharmaceutical preparation using BCP, MO, ECR and ARS reagents.

Reagent	Sample	Proposed (RNH); µg mL^{-1}		Official (RNH); µg mL^{-1}		% Recovery		SD* (RSD)*	SD** (RSD)**
		Taken	Found	Taken	Found	Proposed	Official		
BCP	Aciloc	50.00	50.19	10.00	9.75	100.4	97.50	0.053 (0.106)	0.11 (1.128)
		100.00	100.5			100.5		0.082 (0.086)	
		150.00	150.15			100.1		0.038 (0.026)	
MO		50.00	49.77			99.54		0.072 (0.145)	
		100.00	99.88			99.88		0.064 (0.064)	
		150.00	149.85			99.90		0.042 (0.028)	
ECR		50.00	50.16			100.3		0.066 (0.132)	
		80.00	80.24			100.3		0.072 (0.090)	
		100.0	100.56			100.6		0.049 (0.049)	
ARS		50.00	49.88			99.76		0.083 (0.166)	
		80.00	79.85			99.81		0.079 (0.099)	
		100.00	99.89			99.89		0.056 (0.056)	

Proposed method.*
** Official method.

Table. 4: Inter– and Intra-days precision of the determination of RNH using BCP, MO, ECR and ARS reagents.

Drug	Reagent used	Taken µg mL^{-1}	Inter-day				Intra-day			
			Found µg mL^{-1}	Recovery(%)	SD*	RSD (%)*	Found µg mL^{-1}	Recovery (%)	SD*	RSD (%)*
Pure Solution	**BCP**	50.00	49.84	99.68	0.72	1.48	49.92	99.84	0.65	0.95
		100.0	100.15	100.2	0.62	0.70	99.92	99.92	0.54	0.51
		150.0	149.90	99.93	0.48	0.33	149.8	99.89	0.43	0.41
	MO	50.00	49.54	99.08	0.87	1.18	49.65	99.30	0.70	1.32
		100.0	99.95	99.95	0.70	0.56	100.1	100.1	0.64	0.78
		150.0	150.10	100.1	0.61	0.35	150.1	100.0	0.71	0.29
	ECR	50.00	49.98	99.96	0.42	1.25	50.04	100.08	0.82	1.12
		80.00	79.92	99.92	0.65	0.50	79.83	99.82	0.72	0.58
		100.0	100.07	100.1	0.39	0.42	99.95	99.95	0.65	0.39
	ARS	50.00	49.87	99.74	0.53	0.98	49.84	99.68	0.72	1.32
		80.00	80.09	100.1	0.36	1.17	79.89	99.86	0.62	0.78
		100.0	99.89	99.89	0.81	1.03	100.1	100.1	0.48	0.29
Aciloc Tablet	**BCP**	50.00	50.04	100.1	0.48	1.68	49.74	99.48	0.42	1.40
		100.0	99.96	99.96	0.56	0.94	99.95	99.95	0.66	1.07
		150.0	149.92	99.95	0.75	0.83	150.0	99.99	0.88	0.98
	MO	50.00	49.75	99.50	0.33	1.11	50.05	100.1	0.38	1.29
		100.0	99.93	99.93	0.56	0.93	99.88	99.88	0.45	0.77
		150.0	149.89	99.93	0.91	1.01	149.9	99.95	0.87	0.97
	ECR	50.00	49.95	99.90	0.52	1.19	49.94	99.88	0.90	1.23
		80.00	79.93	99.91	0.66	0.87	79.89	99.86	0.73	0.68
		100.0	99.94	99.94	0.41	0.30	100.1	100.1	0.48	0.37
	ARS	50.00	49.74	99.48	0.74	0.92	50.07	100.1	0.38	0.28
		80.00	79.96	99.95	0.59	0.55	79.95	99.94	0.54	0.71
		100.0	99.92	99.92	0.63	1.11	99.88	99.88	0.81	1.49

* The average of four replicates.

Method validation

Linearity

Under optimum experimental conditions for determination of RNH drug under investigation, the absorbance versus concentration plots were found to be linear over the concentration ranges stated in Table (2). The regression parameters calculated from the calibration graphs data, along with the standard deviations of the slope (m) and the intercept (z) are presented in Table (2). The linearity of the calibration graphs was demonstrated by the high values of the correlation coefficient (r) and the small values of the intercepts of the regression equations. The molar absorptivity and Sandell sensitivity are also shown in Table (2).

Accuracy and precision

In order to determine the precision of the proposed method, the results of the assay of the studied drug in pharmaceutical preparation were compared with the official method (Ruiz et al 2001). Intra- and inter-day precisions were assessed using three concentrations of RNH were prepared and analyzed in four replicates and the analytical results are summarized in Table (4). The low values of the relative standard deviation (%RSD) indicate the high precision and the good accuracy of the proposed method. RSD (%) and SD values were obtained within the same day to evaluate repeatability (inter-day precision) and over four days to evaluate intermediate precision (intra-day precision).

Limits of detection (LOD) and Quantitation (LOQ)

Sensitivity of the method can be determined, through the limit of detection (LOD) and limit of quantification (LOQ). The LOD for the proposed methodwas calculated using the following equation (Basavaiah and Abdulrahman 2010)

$$LOD = 3.3\times\sigma/S$$

Were σ is the standard deviation of replicate determination values and S is the slope of the calibration graph.

The LOQ defined as (Basavaiah and Abdulrahman 2010)

$$LOQ = 10\times\sigma/S$$

Based on the above equations, the limits of detection and quantification were calculated and recorded in Table 1.

Quantification

Under the specified reaction conditions, the molar absorptivity at λ_{max} was found to be a function of concentration of the investigated drug. Beer's law plots were linear with small intercept values (0.011–0.059), slopes ranged from 0.005 to 0.007 in the concentration ranges presented in Table 2. The correlation coefficient, intercepts and regression equation for the proposed procedures were derived using the least-squares method (Saleh et al 2001) (Table 3). The apparent molar absorptivities found to be in the order of 1.78×10^3, 1.65×10^3, 3.43×10^3 and 1.73×10^3 $Lmol^{-1}cm^{-1}$ with the Sandell sensitivities of 0.813, 0.462, 0.541 and 0.630 μg cm^{-2} as calculated from Beer's law (Table 2). The correlation coefficients of the data obtained are 0.9991, 0.9996, 0.9993 and 0.999 for RNH with BCP, MO, ECR and ARS reagents, respectively. Beer's law is obeyed over the concentration ranges of 5–200, 20-350, 10-150 and 10-180 μg mL^{-1} for BCP, MO, ECR and ARS, respectively. It is clear from these data that the tabulated values did not exceed the calculated values indicating no significant differences between the proposed and official methods.

CONCLUSION

Simple, sensitive, accurate and precise spectrophotometric method was developed for the determination of RNH in pure form and pharmaceutical preparation. It was based on ion pair formation and further spectrophotometric determination at 408, 420, 330 and 326 nm for BCP, MO, ECR and ARS reagents, respectively. Thus the method was useful for quality control and routine analysis of RNH. All the analytical reagents used are inexpensive, have good shelf life and are available in any analytical laboratory.

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