Eclética Química
ISSN: 0100-4670
atadorno@iq.unesp.br
Universidade Estadual Paulista Júlio de Mesquita Filho
Brasil

Basavaiah, K.; Somashekar, B.C.
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Eclética Química, vol. 32, núm. 1, 2007, pp. 19-26
Universidade Estadual Paulista Júlio de Mesquita Filho
Araraquara, Brasil

ECLÉTICA Química
www.scielo.br/eq
Volume 32, número 1, 2007

Argentimetric assay of ranitidine in bulk drug and in dosage forms

K. Basavaiah , B.C. Somashekar*
Department of Chemistry, University of Mysore, Manasagangotri, Mysore-570006, India
*E-mail address: * basavaiahk@yahoo.co.in*

Abstract: Two simple, rapid and cost-effective methods based on titrimetric and spectrophotometric techniques are described for the assay of RNH in bulk drug and in dosage forms using silver nitrate, mercury(II)thiocyanate and iron(III)nitrate as reagents. In titrimetry, an aqueous solution of RNH is treated with measured excess of silver nitrate in HNO_3 medium, followed by determination of unreacted silver nitrate by Volhard method using iron(III) alum indicator. Spectrophotometric method involve the addition a known excess of mercury(II)thiocyanate and iron(III)nitrate to RNH, followed by the measurement of the absorbance of iron(III)thiocyante complex at 470 nm. Titrimetric method is applicable over 4-30 mg range and the reaction stoichiometry is found to be 1:1 (RNH: $AgNO_3$). In the spectrophotometric method, the absorbance is found to increase linearly with concentration of RNH which is corroborated by the correlation coefficient of 0.9959. The system obey Beer's law for 5-70 μg mL^{-1}. The calculated apparent molar absorptivity and sandell sensitivity values are found to be 3.27×10^3 L mol^{-1} cm^{-1}, 0.107 μg cm^{-2} respectively. The limits of detection and quantification are also reported for the spectrophotometric method. Intra-day and inter-day precision and accuracy of the methods were evaluated as per ICH guidelines. The methods were successfully applied to the assay of RNH in formulations and the results were compared with those of a reference method by applying Student's t and F-tests. No interference was observed from common pharmaceutical excipients. The accuracy of the methods was further ascertained by performing recovery tests by standard addition method.

Keywords: Ranitidine; assay; silver nitrate; pharmaceuticals; spectrophotometry; titrimetry.

Introduction

Ranitidine hydrochloride (RNH), chemically, is N, N-dimethyl-5-[2-(1-methylamino-2-nitrovinyl)-ethylthiomethyl] furfurylamine hydrochloride (Fig. 1). It is a H_2- receptor antagonist and is widely used in short term treatment of duodenal ulcer and in the management of hypersecretory conditions[1]. The drug is official in Indian Pharmacopoeia[2]. Several techniques such as proton magnetic resonance spectroscopy [3], near infrared reflectance spectroscopy[4,5], scintillation proximity assay[6], flow injection fluorimetry[7,8], polarography[9,10], differential pulse polarography[11], capillary electrophoresis[12], liquid chromatography[13], high performance liquid chromatography [14-18] and kinetic spectrophotometry[19] have been reported for the determination of RNH in pharmaceuticals. These techniques require sophisticated instruments and expensive reagents and involve several manipulation steps.

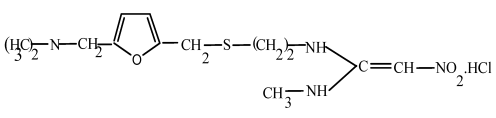


Figure 1. Structure of drug

Literature survey revealed that the only titrimetric method[20] reported for RNH requires 300 mg of drug for each titration. There are several reports of the determination of RNH by spectrophotometry involving the use of Folin-Ciocalteu reagent[21], azine[22] and other[23] dyes, 3-methyl-2-benzothiazoline hydrazone-iron (III)[24], 7, 7, 8, 8 tetracyanoquinodimethane[25], 2, 6-dichloroquinone chlorimide[26], sodium nitrite[27], rose bengal[28], bromothymol blue[29], iodine-

Table 1. Comparison of the existing spectrophotometric methods with the proposed metho for ranitidine

Sl. No.	Reagent/s employed	Linear range, μg mL^{-1} (∈, L mol^{-1} cm^{-1})	**Remarks**	Ref
1.	F-C reagent	40 – 240	Least sensitive	21
2.	$KMnO_4$/NBS-azine dyes	5-30 ($5.2x10^3$) 0.5-4 ($1.89x10^4$) 0.4-2.8 ($4.2x10^4$) 0.4-2.8 ($7.2x10^4$)	Involves extraction	22
3.	Cerium(IV)-chromotrope 2R Cerium(IV)-rhodamine 6G	0.1-2.8 ($1.91x10^5$) 0.1-2.6 ($1.74x10^5$)	Involve boiling for 5 min	23
4.	Iron-(III) MBTH	5 – 18	Involves 30 min contact time, uses an expensive reagent	24
5.	TCQD	1 – 6	Requires thermostating at 70° C for 10 min	25
6.	DCBC	10 – 50	Involves boiling for 20 min	26
7.	$NaNO_2$	0.3 – 12 mg mL^{-1}	Involves flow injection automated assembly, least sensitive	27
8.	Rose bengal	2 – 12	Involves extraction and strict pH control	28
9.	Bromothymol blue	1 – 20	Involves extraction and strict pH control	29
10.	K IO_3^- starch	10 – 80 ($1.8x10^5$)		30
11.	KIO_3 . DCF	5 – 50 ($3.9x10^3$)	Requires strict pH control	31
12.	$Hg(SCN)_2$-iron(III)	5-70 ($3.27 x10^3$)	Applicable to wide dynamic linear range	Present method

F.C.Folin-Ciocalteau; MBTH.3-methyl-2-benzothiazolinone hydrazone; TCQD. Tetracyanoquinodimethane; DCBC.Dichloro-p-benzoquinone chlorimide; DCF. dichlorofluorescein; NBS. N-bromosuccinimide

starch[30] and iodate-dichlorofluorescein[31]. These methods are based on redox, coupling, charge-transfer complexation, nitrosation and ion-pair complexation reactions. However, the reported spectrophotometric methods suffer from one or the disadvantage such as poor sensitivity, a complicated and time consuming procedure, heating or extraction step or the need for expensive or undesirable chemicals (Table 1).

In this communication, we demonstrate the use of titrimetric and spectrophotometric techniques for the determination of RNH. These would overcome the problems encountered in the methods previously mentioned. The titrimetric method involves the addition of measure excess of silver nitrate to RNH in nitric acid medium and back titrating the unreacted silver nitrate with ammonium thiocyanate in the presence of iron(III) alum as the indicator. The spectrophotometric method is based on the displacement of thiocyanate from mercury(II)thiocyanate by the dissociated chloride ion of RNH and liberated thiocyanate reacts with iron(III) to form red colored complex and measurement of complex at 470 nm.

Experimental details

Apparatus

A Systronics model 106 digital spectrophotometer with 1-cm matched quartz cells was used for all absorbance measurements.

Reagents and materials

All chemicals used were of analytical grade. Double distilled water, second time distilled over alkaline potassium permanganate was used throughout.

Silver nitrate solution. An approximately 0.01 mol L^{-1} silver nitrate solution was prepared by dissolving about 0.42 g of $AgNO_3$ (Sarabhai Chemicals, Vadodara) in water and diluting to volume in a 250 mL standard flask. The solution was standardized against sodium chloride[32]. The solution was stored in amber colored bottle and kept in dark untill use. Working solutions were prepared by appropriate dilution when required.

Ammonium thiocyanate solution.An approximately 0.01 mol L^{-1} ammonium thiocyanate solution was prepared by dissolving about 0.38 g of chemical (Ranbaxy Chemicals, New Delhi, India) in water and diluting to 500 mL in a volumetric flask, and standardized by Volhard method[32] and used in titrimetric analysis.

*Iron(III) indicator.*Prepared by dissolving about 10 g of ferric ammonium sulphate in 100 mL of 1:1 nitric acid and boiling the solution till the oxides of nitrogen were expelled.

Iron (III) nitrate reagent. Prepared by dissolving 15.1 g of chemical (BDH) in 45 mL of 72% perchloric acid and diluting to 100 mL with water. This solution was 0.375 mol L^{-1} in iron (III) and 5.25 mol L^{-1} in perchloric acid, and used in spectrophotometric study.

Mercury(II)thiocyanate solution. A saturated solution of mercury(II) thiocayanate solution (Loba Chemie, Mumbai) in methanol was prepared in the usual way. Chloride free nitrobenzene was used for titrimetric work.

1:1 Nitric acid. A 1:1 nitric acid (S.D. Fine Chem. Boisar. India) was prepared by diluting nitric acid with equal volume of water.

Standard RNH solution. Pharmaceutical grade RNH reported to be 99.8% pure was received from Glaxo Smithkline Pharmaceuticals ltd., Nasik, India as gift and was used as received. A stock standard solution of RNH containing 2 mg mL^{-1} was prepared by dissolving 500 mg of sample in water and diluting to 250 mL in a volumetric flask. For spectrophotometric work this concentration was diluted stepwise to get a working solution of 200 µg mL^{-1}.

Sample solution. A quantity of finely ground tablet powder or an aliquot of injection solution equivalent to 200 mg of RNH was accurately transferred into a 100 mL calibrated flask, 60 mL of water added and shaken for 20 min. Then the volume was made up to the mark with water, mixed well, and filtered using a Whatman No 42 filter paper. First 10 mL portion of the filtrate was discarded and a suitable aliquot of the subsequent portion (2 mg mL^{-1} RNH) was taken for assay by titrimetric procedure. The filtrate(tablet extract/injection) was diluted appropriately to get 200 µg mL^{-1} solutions for spectrophotometric determination.

Dosage forms. The fallowing dosage forms were purchased from local commercial sources and subjected to analysis.

Zintac tablets (300 mg) and ranitidine injections (25 mg) both from Torrent Pharmaceuticals, Ltd., India, and aciloc tablets (150 mg) and injections (25 mg) from Glaxo smithkline Pharma. Ltd., India.

Procedures

Titrimetry. An aliquot measuring 15 mL of standard solution containing 4-30 mg RNH was measured accurately into a 100 mL Erlenmeyer flask and acidified with 2 mL of 1:1 nitric acid. Then, 10 ml of 0.01 mol L^{-1} silver nitrate was introduced by means of a pipette and shaken thoroughly for a min. Finally, 2 mL of nitrobenzene were added and shaken vigorously until the silver chloride was coagulated; 0.5 mL of iron(III) alum indicator was added and the residual silver nitrate was titrated with standard 0.01 mol L^{-1} ammonium thiocyanate solution to a permanent red color end-point. A blank was run in the same way.

The drug content was calculated using the formula

$$\frac{(B-S)\ R\ Mw}{n}$$

where B is the volume of thiocyanate consumed in the blank titration,
S is the volume of thiocyanate consumed in the test sample titration,
R is the molarity of thiocyanate solution,
Mw is the relative molecular mass of drug and 'n' is the number of moles of silver nitrate reacting with one mole of drug.

Spectrophotometry. Into a series of 10 mL standard flasks were transferred 0,0.25, 0.5, 1.0, ……3.5 mL of 200 µg mL^{-1} of RNH solution by means of a microburette; 2 mL of mercury(II) thiocyanate solution and 1 mL of iron (III) nitrate reagent were added and diluted to volume with water. The solution was mixed well and absorbance measured against the reagent blank at 470 nm after 10 nm. The increase in absorbance was plotted against the RNH concentration. The concentration of the unknown was read from the calibration graph or computed from the linear regression equation.

Convenient aliquot of tablet/injection solutions (2 mg mL^{-1} for titrimetry and 200 µg mL^{-1} for spectrophotometry were subjected to analysis by the above procedures.

Results and Discussions

Majority of the pharmaceutically important organic compounds are prepared as hydrochlorides and some have been assayed by determining their chloride content. No literature reports were found describing the assay of RNH *via* determination of its chloride content. The present work deals with the determination of RNH by two methods. In titrimetry, the drug was determined by measuring its chloride content by Volhard method[32]. The spectrophotometric procedure involves the reaction of chloride with mercury (II) thiocyanate to form soluble mercury(II)chloride with the liberation of thiocyanate ions which then react with iron (III) to form the familiar red colour which can be measured at 470 nm.

Method development

Titrimetry

Volhard method has been used for the indirect determination of chloride in diverse matrices including pharmaceuticals[33,34]. In the present method, a known excess of standard silver nitrate solution is added to the drug solution and the excess back titrated with standard thiocyanate solution using iron(III) as indicator and in the presence of nitrobenzene. RNH in aqueous solution ionizes to give the protonated drug moiety and chloride ion, the latter being reacted with Ag^+ as follows:

$$RNH.HCl \rightleftharpoons RNH^+ + Cl^-$$

$$Cl^- + Ag^+ \text{ (excess)} \rightleftharpoons AgCl(s) + Ag^+ \text{ (unreacted)}$$

$$Ag^+ \text{ (unreacted)} + SCN^- \rightleftharpoons AgSCN(s)$$

Iron (III) serves as the indicator imparting a red color to the solution to the first excess of thiocyanate ion:

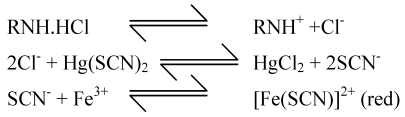
$$Fe^{3+} + SCN^- \rightleftharpoons Fe\ SCN^{2+} \text{ (red)}$$

A 0.5 mL of indicator solution and 2 mL of 1:1 nitric acid in a total volume of about 30 mL gave satisfactory results. AgCl is more soluble than AgSCN and hence leads to low values of chloride analysis and drug recovery. This source of error is circumvented by the addition of 2 mL of nitrobenzene and shaking the reaction mixture thoroughly before the back titration of the residual silver nitrate[35]. The calculated molar ratio of 1:1 between RNH and $AgNO_3$ is consistent with the reaction scheme shown above and was used for calculations.

Spectrophotometry

There are several reports on the spectrophotometric determination of chloride in various matrices[36-40]. One of the most widely used methods for the determination of chloride at low

levels consists of spectrophotometric measurement at 470 nm of the coloured iron (III) thiocyanate complex[36-40]. In the proposed method, the dissociated chloride of RNH displace thiocyanate from mercury(II)thiocyanate and the liberated thiocyanate reacts with iron(III) to form red coloured complex $FeSCN^{2+}$ which is measured at 470 nm. The essential reaction involved are:



The absorbance of the coloured complex measured is a quantitative measure of the concentration of RNH. The wavelength of maximum absorption was found at 470 nm which is in agreement with the earlier observations in perchloric acid medium [36,37]. The linear increase in absorbance at 470 nm with increase in RNH concentration showed that the protonated drug moiety, RNH^+ had no effect on the complex formation and its colour stability.

Since the method is essentially the measurement of iron (III) thiocyanate complex, different variables like the kind of acid, source of iron (III), excess of thiocyanate and contact time which influence the colour intensity and the stability were optimised.

The effect of varying concentrations of HNO_3, $HClO_4$ and H_2SO_4 on the absorbance was studied. HNO_3, $HClO_4$ gave similar sensitivities while the use of H_2SO_4 led to a much lower sensitivity. Perchloric acid was chosen as the reaction medium in preference to nitric acid for lower blank absorbance, and because low and erratic results were obtained with nitric acid. The effective perchloric acid concentration employed was about 0.5 mol L^{-1}.

Different sources of iron (III) may be used, such as iron(III) nitrate[37], iron (III) ammonium sulphate[39] perchlorate[36]. Iron(III)nitrate was preferred to the other iron (III) salts, because the procedure using iron (III) nitrate was found to be more sensitive and more linear than that using iron (III) ammonium sulphate and because of high chloride content of iron (III) perchlorate. One milliliter of iron (III) nitrate solution in a total volume of 10 mL was found adequate. Higher concentrations were found to increase the absorbance only slightly but larger blanks were obtained. With increasing concentrations of mercury (II)thiocyanate, increase in absorbance was only marginal. Two mL of reagent solution in a total volume of 10 mL was found sufficient.

Different solvents such as ethanol[37], methanol[40] and water[36] have been used to prepare mercury(II)thiocyanate reagent. High sensitivity was obtained when methanolic solution was used. Moreover, large amounts of ethanol are reported to bleach the iron(III)thiocyanate complex[36]. The reaction is fast and colour development is considered complete in 5 min at room temperature (30±2°C). The colour remained stable up to 6 h.

Method Validation

Quantitative parameters

Titrimetry was found applicable in the range 4-30 mg, outside which the results were not satisfactory. The relationship between the titration end-point obtained by the proposed titrimetric method and the drug amount was examined. The linearity between the amount of drug and titration end-point is apparent form the calculated best-fit line *via* linear least squares treatment. The calculated value of r(0.9974) shows that the reaction between $AgNO_3$ and RNH proceeds stoichiometrically in the ratio 1:1.

Under the described experimental conditions, a linear correlation was obtained between absorbance (A) and the concentration (C) of RNH over the range 5-70 μg mL^{-1}. The linear regression equation was:

$$A = 0.0046 + 0.0091\ C \qquad (r=0.9959)$$

The apparent molar absorptivity and Sandell's sensitivity were 3.27 x 10^3 L mol^{-1}.cm and 0.107 μg cm^{-2}, respectively.

The limits of detection (LOD) and quantification (LOQ) were calculated according to the current ICH guidelines (41) using the fallowing formulae:

$$LOD = \frac{3.3\ \sigma}{S} \quad \text{and} \quad LOQ = \frac{10\ \sigma}{S}$$

where σ is the standard deviation of seven reagent blank determinations and S is the slope of the calibration curve. The calculated LOD and LOQ were found to be 0.86 and 2.61 μg mL^{-1}, respectively.

Accuracy and precision

The accuracy of the methods was evaluated by analyzing the pure drug at different levels and the precision was established by determining the relative standard deviation of seven replicate analysis on the same solution containing three different levels of the drug. The percentage recovery, the RSD and the range of error (%) at 95% confidence level indicate the reasonable accuracy and precision of the methods.

The values of between-day RSD for three different concentrations of drug, obtained from determinations carried out over a period of five days were between 2.5-4.0% indicating the reasonable repeatability of the methods (Table 2).

The ruggedness/robustness of the methods was assessed by calculating the RSD for results obtained by performing the analysis using three different instruments and by three different persons. The inter-instrumental RSD values were in the range of 3.5 – 5.5 whereas the inter-personal RSD values varied from 2.6-4.2 (n= 3 in both instances) for three concentrations employed for accuracy and intra-day precision studies.

Interferences

Bromide ion interferes in any quantity. Higher concentration of sulphates and phosphates bleach the colour of iron (III) thiocyanate complex. Large amounts of ethyl and isopropyl alcohols are reported to impart a yellowish brown colour to the complex. But none of the above substances is present in either the reagents employed or the formulations analysed, and hence the methods are devoid of error due to them.

Application to analysis of tablets and injections

The proposed methods were applied to the determination of RNH in tablets and injections. The results presented in Table 3 indicate that excipients present in formulations do not interfere with the visual end-point detection and spectrophotometric measurement of iron(III)thiocyanate complex. The same batch of tablets were also assayed by a reference method[2] which consisted of the measurement of the absorbance of the tablet extract or injection solution in 0.1 mol L^{-1} hydrochloric acid at 225 nm, and statistical analysis (t- and F-test) of the results obtained by the proposed methods and the reference method showed no significant difference in the performance of the two methods.

Recovery study

To confirm the accuracy and reliability of the methods recovery test was performed *via* standard-addition procedure. Pre-analysed tablet powder/injection solution containing a known and definite amount of RNH was spiked with pure drug at three levels and the total was found by the proposed methods. The percent recovery of added pure drug which lies between 98.2 and 103.6 (Table 4) reveals that the procedures are free from interference from usual tablet excipients like talc, starch, state, alginate, gumacacia, calcium gluconate, sucrose, etc.

Conclusions

The method using $AgNO_3$ is indirect and is based on the determination of the chloride of

Table 2. Accuracy and precision of the methods

Titrimetric method						Spectrophotometric method					
RNH taken, mg	RNH found*, mg	Error, %	RSD[a], %	RSD[b], %	Range of error, %	RNH taken, µg mL^{-1}	RNH found*, µg mL^{-1}	Error, %	RSD[a], %	RSD[b], %	Range of error, %
5	4.86	2.8	1.29	3.2	±1.29	20	20.53	2.65	1.10	4.0	±1.10
15	14.68	2.13	1.65	2.5	±1.64	40	39.02	2.45	0.97	2.9	±0.97
25	24.26	2.96	0.94	2.8	±0.95	60	58.69	2.18	0.97	3.8	±0.96

*Values obtained for seven determinations.
a is intra-day precision
b is inter –day precision

Table 3. Results of determination of RNH in tablets

Tablet/injection brands[ψ]	Label claim, mg/tablet or mL	% found* ± SD		
		Titrimetry	Spectrophotometry	Reference method
Tablets	300	98.6±1.01	101.6±1.02	99.71±1.36
Zintac[a]		t=1.47	t=2.52	
		F=1.81	F=1.78	
Aciloc[b]	150	101.8±1.02	100.4±1.16	102.66±1.04
		t=1.32	t=3.25	
		F=1.04	F=1.24	
Injections		99.8±0.78	99.1±1.34	101.75±1.26
Ranitidine[a]	25	t=3.02	t=3.22	
		F=2.61	F=1.13	
Aciloc[b]	25	100.5±0.95	98.4±0.52	99.28±1.06
		t=1.92	t=1.76	
		F=1.24	F=4.16	

* Average of five determinations;
[ψ] Marketed by: a. Torrent Pharmaceuticals Ltd.; b. Glaxo SmithKline Pharm Ltd.
Tabulated t-value at 95% confidence level is 2.77.Tabulated F-value at 95% confidence level is 6.39

Table 4. Results of recovery test

Formulation examined	Titrimetry				Spectrophotometry			
	RNH in tablet, mg	Pure RNH added, mg	Total found, mg	Recovery* of pure RNH added, %	RNH in tablet, µg mL^{-1}	Pure RNH added, µg mL^{-1}	Total found, µg mL^{-1}	Recovery* of pure RNH added, %
Aciloc (150	10.18	5	15.26	101.6	20.08	10	30.44	103.6
mg)	10.18	10	20.40	102.2	20.08	20	40.04	99.8
	10.18	15	25.21	100.2	20.08	40	60.20	100.3
Injection	10.05	5	15.03	99.6	19.68	10	29.89	102.1
Aciloc	10.05	10	19.89	98.4	19.68	20	39.32	98.2
(25 mg)	10.05	15	25.25	101.3	19.68	40	59.76	100.2

* Mean value of three determinations.

the dissociated RNH in solution. The method is rapid, covers a wide range(4-30 mg) of determination and employed unreduced RNH for assay. The spectrophotometric method is reasonably sensitive($\in = 3.27 \times 10^3$ L $mol^{-1}cm^{-1}$) but uses a novel reaction. Applicable over a wide linear dynamic concentration range, it involves the measurement of highly coloured species which can be regarded as an additional advantage.

The titrimetric method calls for exercising care while handling nitrobenzene which is appreciably toxic. Similar care is needed when mercury(II) thiocyanate is used in the spectrophotometric method. But, both methods are free from interference from concomitant substances. However, the serious limitations of both procedures is the lack of specificity, since the methods can be used only when it is absolutely certain that all the chloride ion being determined comes from RNH in question. The applications of these methods are usually restricted to quality control procedures and to the analysis of solution and tablets containing no interfering chloride.

Acknowledgements

The authors express their gratitude to the Quality Control Manager, Glaxo SmithKline Pharmaceuticals, Nasik, India, for providing pure ranitidine as gift. One of the authors (BCS) thanks the authorities of the University of Mysore, Mysore, for research facilities.

Received 25 September 2006.
Accepted 07 February 2007.

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