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Determination of ranitidine hydrochloride in pharmaceutical preparations by titrimetry and visible spectrophotometry using bromate and acid dyes

K. Basavaiah *, P. Nagegowda

Department of P.G. Studies and Research in Chemistry, University of Mysore, Manasagangotri, Mysore 570 006, India

Abstract

Four new methods using titrimetry and spectrophotometry are described for the determination of ranitidine hydrochloride (RNH) with potassium bromate as the oxidimetric reagent and acid dyes, methyl orange, indigo carmine and metanil yellow. In direct titrimetry (method A), the drug is titrated directly with bromate in acid medium and in the presence of excess of bromide using methyl orange indicator. In back titrimetry (method B), the drug is treated with a measured excess of bromate in the presence of bromide and acid, and the unreacted bromine is determined iodometrically. Both spectrophotometric methods are based on the oxidation of RNH by a known excess of bromate in acid medium and in the presence of excess of bromide followed by estimation of surplus oxidant by reacting with either indigo carmine (method C) or metanil yellow (method D), and measuring the absorbance at 610 or 530 nm. In methods B, C and D, reacted oxidant corresponds to the drug content. The experimental conditions are optimized. Titrimetric procedures are applicable over the ranges 1–10 mg (A) and 1–17 mg (B), and the reaction stoichiometry is found to be 1:1 (BrO_3^-: RNH). In spectrophotometric methods, the absorbance is found to increase linearly with increasing concentration of RNH, which is corroborated by the calculated correlation coefficient (r) of 0.9984 (C) and 0.9976 (D). The systems obey Beer's law for 2–12 and 1–7 µg ml^{-1}, for methods C and D, respectively. Method D with a molar absorptivity of 9.82×10^4 l mol^{-1} cm^{-1} is found to be more sensitive than method C ($\varepsilon = 2.06 \times 10^4$ l mol^{-1} cm^{-1}). The limits of detection and quantification are reported for both the spectrophotometric methods. The proposed methods were applied successfully to the determination of RNH in tablets and injections. The reliability of the assay was established by parallel determination by the official method and by recovery studies.

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Keywords: Ranitidine; Titrimetry; Spectrophotometry; Bromate; Acid dyes; Pharmaceuticals

1. Introduction

Ranitidine hydrochloride (RNH) is chemically N-[2-[[[-5-[(Dimethylamino)methyl]-2-furanyl]methyl]thio]ethyl]-N′-methyl-2-nitro-1,1-ethenediamine hydrochloride. It is an H$_2$-receptor antagonist and is widely used for the short-term treatment of duodenal ulcer and for the management of hypersecretory conditions [1]. Methods available in the literature for the determination of RNH in pharmaceutical preparations include proton magnetic resonance spectroscopy [2], near infrared reflectance spectrometry [3], scintillation proximity assay [4], flow-injection fluorimetry [5], polarography [6,7] differential pulse polarography [8], capillary electrophoresis [9], high-performance liquid chromatography [l0–14] and liquid chromatography [15].

Literature survey reveals that the only titrimetric procedure reported for RNH [16] requires 300 mg of sample for each titration. Spectrophotometric methods for the determination of RNH have been suggested based on the use of suitable chromogenic reactions with Folin-Ciocalteu reagent [17], azine dyes [18], 3-methyl-2-benzothiazoline hydrazone-iron (III) [19,20], 3,5-dichloro-*p*-benzoquininone chlorimine [21], sodium nitrite [22], Rose Bengal [23] and bromothymol blue [24]. These methods involve redox, coupling, charge-transfer complexation, nitrosation and ion-associate reactions.

Recently, spectrophotometric methods based on redox [25,26] and charge-transfer complex [27] formation reactions have been suggested for the determination of RNH in pure drug and dosage forms including in the presence of oxidative degrades [25].

This paper describes four simple, accurate, precise and sensitive methods for the determination of RNH in pure

* Corresponding author.
E-mail address: basavaiahk@yahoo.co.in (K. Basavaiah).

sample and pharmaceutical preparations. The methods use bromine-generated in situ as the oxidizing agent and three dyes as either indicator or spectrophotometric reagents.

2. Experimental

2.1. Apparatus

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

2.2. Reagents

All the reagents used were of analytical-reagent grade, and doubly distilled water was used throughout.

2.2.1. Potassium bromate
A 0.01 mol l^{-1} solution was prepared by dissolving 1.67 g of the salt in water and diluting to 1 l in a volumetric flask and used for indirect titrimetry. The solution was diluted appropriately with water to get 0.005 mol l^{-1}, 30 and 25 µg ml^{-1} solutions for methods A, C and D, respectively.

2.2.2. Indigo carmine for method C
A 1000 µg ml^{-1} solution was prepared by dissolving 112 mg of dye (90% purity) in water and diluting to 100 ml in a volumetric flask. This was further diluted 10-fold to get a working concentration of 100 µg ml^{-1}.

2.2.3. Metanil yellow for method D
A 1000 µg ml^{-1} solution was prepared by dissolving 117 mg of dye (85% dye content) in water and diluting to 100 ml in a volumetric flask. This was appropriately diluted to get a working concentration of 40 µg ml^{-1}.

Aqueous solutions of potassium bromide (10%), potassium iodide (10%), sodium thiosulphate (0.06 mol l^{-1}), hydrochloric acid (5 mol l^{-1}), methyl orange indicator (0.05%) and starch indicator (1%) were prepared in the usual way.

2.2.4. RNH and its formulations
Pharmaceutical grade RNH was kindly gifted by Glaxo Smithkline Pharmaceuticals Ltd., Mumbai, India, and used as received. Formulations containing RNH were purchased from local commercial sources. Stock standard solution containing 2 mg ml^{-1} drug was prepared by dissolving the weighed amount of RNH in water and kept in an amber coloured bottle and stored in a refrigerator. Working solutions (40 µg ml^{-1} for method C and 20 µg ml^{-1} for method D) were prepared whenever required by appropriate dilution of the stock solution with water.

2.3. Procedures

2.3.1. Direct titrimetry (method A)
A 10 ml aliquot of drug solution containing 1–10 mg RNH was transferred into a titration flask by means of a pipette.

One millilitre of 5 mol l^{-1} hydrochloric acid, 5 ml 10% potassium bromide and two drops of methyl orange indicator were added, and titrated with 0.005 mol l^{-1} bromate solution to a colourless end point. An indicator blank titration was run. The amount of the drug was calculated from the amount of titrant reacted.

2.3.2. Back titrimetry (method B)
A 10 ml aliquot of drug solution containing 1–17 mg RNH was placed in a 100-ml stoppered flask. One millilitre of 5 mol l^{-1} hydrochloric acid and 5 ml of 10% potassium bromide were added followed by 10 ml of bromate solution (0.01 mol l^{-1}) by means of a pipette. The flask was stoppered and kept aside for 5 min with occasional shaking. The stopper was then washed with 5 ml of water, and 5 ml of 10% potassium iodide were added to the flask. The liberated iodine was titrated with 0.06 mol l^{-1} thiosulphate using starch as indicator. A blank titration was run under identical conditions.

2.3.3. Spectrophotometry using indigo carmine (method C)
Aliquots of RNH solution (0.5–3.0 ml; 40 µg ml^{-1}) were delivered into a series of 10-ml calibrated flasks by means of a micro burette. To each flask was added 1 ml of 5 mol l^{-1} HCl and the total volume was adjusted to 4 ml by adding water. Then, 2.0 ml of 10% potassium bromide and 1.5 ml of 30 µg ml^{-1} potassium bromate were added, the flasks were stoppered and set aside for 10 min with occasional shaking. Finally, 2 ml of 100 µg ml^{-1} indigo carmine were added to each flask, diluted to volume with water and absorbance measured at 610 nm against a water blank after 5 min.

2.3.4. Spectrophotometry using metanil yellow (method D)
Aliquots of RNH solution (0.5–3.5 ml; 20 µg ml^{-1}) were transferred into a series of 10-ml calibrated flasks by means of a micro burette. Two millilitres of 5 mol l^{-1} HCl were added to each flask and the total volume was brought to 5.5 ml with water. Then, 2.0 ml of 10% potassium bromide and 1.0 ml of 25 µg ml^{-1} potassium bromate solutions were added successively, the flasks were stoppered and let stand for 5 min. Finally, 1 ml of 40 µg ml^{-1} metanil yellow was added to each flask, diluted to volume with water and absorbance measured at 530 nm against a water blank after 5 min.

In either spectrophotometric method, the concentration of the unknown was read from the calibration graph or calculated from the regression equation obtained from Beer's law data.

2.3.5. Assay procedure for formulations
Twenty tablets were weighed and ground into a fine powder. An amount of the powder equivalent to 200 mg of RNH was weighed into a 100-ml volumetric flask, 60 ml water added and shaken thoroughly for about 20 min. The volume was diluted to the mark with water, mixed well and filtered using Whatmann No. 42 filter paper. First 10 ml portion of the filtrate was rejected and a convenient aliquot of filtrate
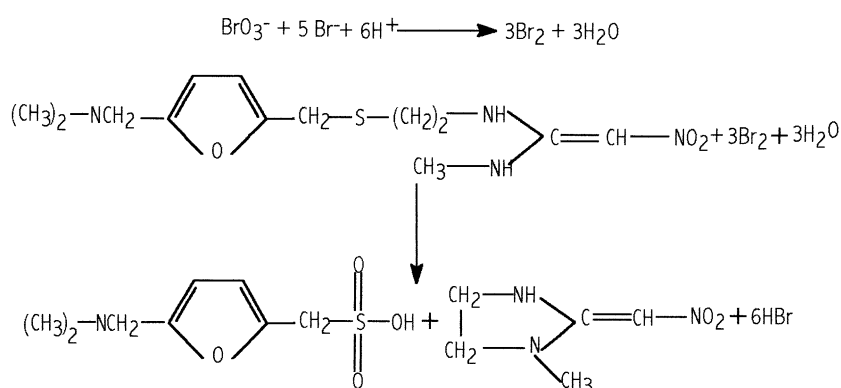
$$BrO_3^- + 5\,Br^- + 6H^+ \longrightarrow 3Br_2 + 3H_2O$$

Fig. 1. Reaction scheme.

(containing 2 mg ml^{-1} RNH) was taken for assay by titrimetric procedures, A and B. The filtrate was diluted stepwise to get 40 and 20 μg ml^{-1} RNH for use in spectrophotometric methods C and D, respectively. A suitable aliquot was then subjected to analysis.

3. Results and discussion

Aqueous bromine solutions are unstable because of the high vapour pressure of bromine. An acidified mixture of bromate and bromide actually behaves as an equivalent solution of bromine, and has been used extensively for the determination of inorganic and organic substances [28]. This solution has been applied for the determination of a large number of substances of pharmaceutical importance by both direct titrimetry [29–44] and indirect titrimetry [45–52] based on oxidation or substitution reactions.

3.1. Titrimetry

The proposed titrimetric procedures are based on the oxidation reaction between RNH and bromine generated in situ. Since the molar ratio of the reaction was found to be 1:1 in both methods (A and B), it is probable that the drug undergoes oxidation as per the reaction scheme given in Fig. 1.

Both direct and indirect titration of RNH was successful in 0.125–0.50 mol l^{-1} hydrochloric acid medium. Of the several dyestuffs tried, methyl orange was found to give a very sharp end point in direct titration and the indicator correction was negligibly small. With 0.005 mol l^{-1} bromate, 1–10 mg of RNH can be conveniently determined. For the range investigated by indirect titrimetry (1–17 mg), the reaction was found to be stoichiometric up to a contact time of 5 min beyond which slightly larger volumes of bromate were consumed but never yielded a definite stoichiometry up to 30 min. This is possibly due to bromination of the drug molecule. Hence, it is necessary that the back titration of the unreacted bromine should be completed immediately after 5 min to get accurate and precise results. The effect of concentration of bromate was also investigated and it was found that a 0.01 mol l^{-1} concentration was the best, as higher

concentrations of the reagent lead to higher results, perhaps caused by loss of bromine. A 10 ml volume of 0.01 mol l^{-1} bromate solution was found adequate for quantitative oxidation of RNH in the range determined. The relation between the amount of the drug and titration end point was examined. The linearity is apparent from the correlation coefficient of 0.9986 (method A) and –0.9863 (method B) suggesting that the reaction between the RNH and bromate proceeds stoichiometrically in the ratio 1:1.

3.2. Spectrophotometry

Many dyes are irreversibly destroyed to colourless species by oxidizing agents in acid medium [28] and this observation has been exploited for the indirect spectrophotometric determination of some bioactive compounds [18,53–56]. In recent years, acidified solution of bromate and bromide, and acid dyes has been adapted to the quantification of several pharmaceuticals [57–59]. In the proposed spectrophotometric methods, the ability of bromine to effect oxidation of RNH and irreversibly destroy indigo carmine and metanil yellow dyes to colourless products [28] in acid medium has been capitalized. Both methods are based on the oxidation of the drug by measured excess of bromine and subsequent determination of the latter by reacting with indigo carmine or metanil yellow, and measuring the absorbance at 610 or 530 nm. In either method, the absorbance increased linearly with increasing concentration of drug.

RNH when added in increasing amount to a fixed amount of bromine consumes the latter and there will be a concomitant decrease in the concentration of bromine. When a fixed amount of either dye is added to decreasing amounts of bromine, a concomitant increase in the concentration of dye is obtained. This is observed as a proportional increase in the absorbance at the respective wavelengths of maximum absorption with increasing concentration of RNH (Figs. 2 and 3).

Preliminary experiments were performed to fix the upper limits of the dyes that could be measured spectrophotometrically, and these were found to be 20 and 4 μg ml^{-1} for indigo carmine and metanil yellow, respectively. A bromate concentration of 4.5 μg ml^{-1} was found to irreversibly destroy the
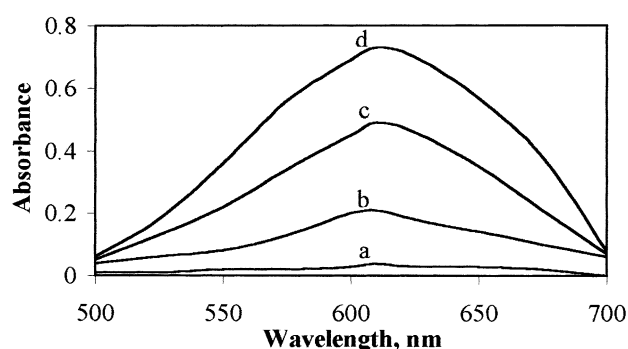
Fig. 2. Absorption spectra of 20.0 µg ml^{-1} indigo carmine in the presence of 4.5 µg ml^{-1} bromate. (a) Without RNH; (b) with 4 µg ml^{-1} RNH; (c) with 8 µg ml^{-1} RNH and (d) with 12 µg ml^{-1} RNH.
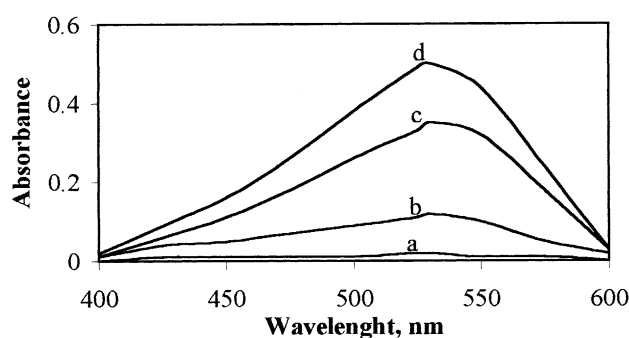

Fig. 3. Absorption spectra of 4.0 µg ml^{-1} metanil yellow in the presence of 2.5 µg ml^{-1} bromate. (a) Without RNH; (b) with 2 µg ml^{-1} RNH; (c) with 4 µg ml^{-1} RNH and (d) with 6 µg ml^{-1} RNH.

Table 1
Optical parameters

Parameter	Method C	Method D
λ_{max} (nm)	610	530
Beer's law limits (µg ml^{-1})	2–12	1–7
Molar absorptivity (1 mol^{-1} cm^{-1})	2.06×10^4	9.82×10^4
Sandell sensitivity (ng cm^{-2})	17.24	12.44
Limit of detection (LOD)[a] (µg ml^{-1})	0.07	0.12
Limit of quantification (LOQ)[b] (µg ml^{-1})	0.21	0.40
Regression equation (Y)[c]		
Slope (b)	0.06 ± 0.29	0.08 ± 0.17
Intercept (a)	0.01 ± 0.05	$-9.1 \times 10^{-3} \pm 0.03$
Correlation coefficient (r)	0.9984	0.9976

[a] Calculated from LOD = $3.3\sigma/S$, where σ is the S.D. of the response and S is the slope of the calibration curve.
[b] Calculated from LOQ = $10\sigma/S$, where σ and S are estimated as done for LOD.
[c] $Y = a + bX$, where Y is the absorbance and X concentration in µg ml^{-1}.

3.3. Analytical parameters

A linear correlation was found between absorbance at λ_{max} and concentration ranges given in Table 1 in both methods. Correlation coefficients, intercepts and slopes for the calibration data are also presented in Table 1. The graphs showed negligible intercept as described by the regression equation,

$$Y = a + bX$$

obtained by the method of least squares. Other sensitivity parameters such as molar absorptivity, Sandell sensitivity and detection limit are also given in Table 1 and indicate the high sensitivity of the methods.

3.4. Accuracy and precision, and ruggedness of the methods

The accuracy of the proposed methods was established by analysing the pure drug in three levels (within working concentration ranges) and the precision was ascertained by calculating the relative standard deviation (RSD) of seven replicate determinations on the same solution containing the drug in three levels. The % error and RSD values (<3%) indicate the high accuracy and precision of the methods (Tables 2 and 3). For a better picture of reproducibility on a day-to-day basis, a series was run in which standard drug solution in three levels was run each day for 5 d. The day-to-day RSD values were in the range of 1.5–3.5%, and represent the best appraisal of the procedures in daily routine use.

3.5. Application

The proposed methods were applied to the assay of RNH in tablets without any coated colour lest it should interfere with the spectrophotometric methods and in injections. The results are compiled in Table 4 and were checked by the

blue colour of 20 µg ml^{-1} indigo carmine, whereas 2.5 µg ml^{-1} oxidant was required to destroy 4 µg ml^{-1} metanil yellow to a colourless product. Hence, different amounts of RNH were reacted with 1.5 ml of 30 µg ml^{-1} bromate in method C, and with 1 ml of 25 µg ml^{-1} bromate in method D, followed by the determination of residual oxidant as described under the respective procedures.

Hydrochloric acid was the medium of choice for the oxidation of the drug by bromate as well as the latter's determination employing the dyes. The absorbance of the dyes was not affected in 0.125–1.25 mol l^{-1} hydrochloric acid concentration. However, since 0.5 and 1.0 mol l^{-1} acid concentrations were found optimum for the oxidation reaction in a reasonable time of 10 and 5 min, in methods C and D, respectively, the same concentration was maintained for the determination of the unreacted bromate with the dyes, and even this reaction time is not critical. Any delay up to 30 min had no effect on the absorbance. A contact time of 5 min is necessary for the complete destruction of the dyes by the residual bromine. Though the colour of acid form of either dye was indefinitely stable in hydrochloric acid medium, it was found to be stable up to 30 min in the presence of the oxidation product of the drug. Hence, the absorbance of the dye solution should be measured within 30 min after its addition.

Table 2
Evaluation of accuracy and precision of titrimetric methods

Method A				Method B			
Amount taken (mg)	Amount found [a] (mg)	Error (%)	RSD (%)	Amount taken (mg)	Amount found [a] (mg)	Error (%)	RSD (%)
3.00	3.05	1.67	2.36	5.00	5.12	2.40	1.86
6.00	5.98	0.33	0.74	10.00	10.03	0.30	0.81
9.00	8.87	1.44	1.28	15.00	15.06	0.41	1.07

[a] Average value of seven determinations.

Table 3
Evaluation of accuracy and precision of spectrophotometric methods

Method C				Method D			
Amount taken (μg)	Amount found [a] (μg)	Error (%)	RSD (%)	Amount taken (μg)	Amount found [a] (μg)	Error (%)	RSD (%)
20.00	20.38	1.90	1.68	40.00	40.81	2.03	2.18
40.00	40.10	0.25	0.24	70.00	69.12	1.26	0.93
60.00	59.48	0.87	1.02	100.00	98.17	1.83	1.67

[a] Average value of seven determinations.

Table 4
Results of analysis of tablets containing RNH by the proposed methods and comparison with the established methods[***]

Brand name [*] and dosage form	Label claim (mg per tablet or per ml)	Found [**] (% recovery ± S.D.)				
		Official method	Method A	Method B	Method C	Method D
Ranitin [a]	150	101.23 ± 1.02	100.28 ± 0.64; $t = 1.81$; $F = 2.54$	101.36 ± 0.74; $t = 0.23$; $F = 1.90$	99.74 ± 0.68; $t = 2.76$; $F = 2.25$	100.96 ± 0.85; $t = 0.46$; $F = 1.44$
	300	97.96 ± 0.85	98.64 ± 0.66; $t = 1.42$; $F = 1.66$	99.04 ± 0.38; $t = 2.77$; $F = 5.00$	98.28 ± 0.64; $t = 0.68$; $F = 1.76$	99.23 ± 1.02; $t = 2.14$; $F = 1.44$
Histac [b]	150	100.62 ± 0.46	101.65 ± 0.95; $t = 2.31$; $F = 4.36$	100.96 ± 0.62; $t = 0.99$; $F = 1.82$	100.10 ± 0.36; $t = 2.00$; $F = 1.63$	101.46 ± 0.67; $t = 2.35$; $F = 2.12$
	300	101.26 ± 0.34	100.83 ± 0.71; $t = 1.29$; $F = 4.36$	101.98 ± 0.78; $t = 2.77$; $F = 1.99$	101.28 ± 1.28; $t = 0.07$; $F = 2.43$	101.66 ± 0.76; $t = 1.45$; $F = 5.00$
Zinetac [c]	150	98.48 ± 1.18	97.56 ± 0.85; $t = 1.43$; $F = 1.93$	100.06 ± 0.87; $t = 2.43$; $F = 1.84$	98.63 ± 0.66; $t = 0.82$; $F = 3.20$	99.35 ± 0.74; $t = 1.43$; $F = 2.54$
	300	102.10 ± 0.81	100.56 ± 0.62; $t = 2.37$; $F = 1.71$	101.48 ± 0.53; $t = 1.46$; $F = 2.34$	102.28 ± 0.85; $t = 0.49$; $F = 1.10$	101.88 ± 1.47; $t = 0.3$; $F = 3.29$
Aciloc [d]	150	98.84 ± 0.74	97.91 ± 0.42; $t = 2.53$; $F = 3.10$	99.35 ± 0.38; $t = 1.44$; $F = 4.54$	99.04 ± 0.44; $t = 0.54$; $F = 2.83$	98.92 ± 0.63; $t = 0.14$; $F = 1.38$
	300	100.08 ± 0.71	98.98 ± 0.64; $t = 2.57$; $F = 1.23$	100.08 ± 0.71; $t = 2.61$; $F = 2.58$	99.62 ± 0.38; $t = 1.33$; $F = 3.49$	100.36 ± 0.85; $t = 0.57$; $F = 1.43$
Injections						
Ranitin [a]	25	98.64 ± 0.38	98.36 ± 0.85; $t = 0.73$; $F = 5.00$	99.42 ± 0.78; $t = 0.6$; $F = 4.21$	98.67 ± 0.67; $t = 0.63$; $F = 3.11$	99.16 ± 0.36; $t = 1.19$; $F = 5.12$
Histac [b]	25	101.18 ± 0.77	100.34 ± 0.72; $t = 1.74$; $F = 1.14$	102.01 ± 1.12; $t = 1.42$; $F = 1.12$	100.41 ± 1.54; $t = 1.82$; $F = 4.00$	101.74 ± 0.86; $t = 1.08$; $F = 1.25$
RNH [c]	25	100.08 ± 1.14	101.12 ± 0.54; $t = 1.74$; $F = 4.46$	98.28 ± 0.78; $t = 1.31$; $F = 2.14$	99.62 ± 0.86; $t = 0.73$; $F = 1.76$	101.36 ± 10.28; $t = 1.67$; $F = 1.26$
Aciloc [d]	25	99.89 ± 0.92	100.13 ± 1.06; $t = 0.38$; $F = 1.33$	98.83 ± 0.67; $t = 2.11$; $F = 1.89$	101.38 ± 1.53; $t = 1.92$; $F = 3.01$	100.74 ± 0.63; $t = 1.73$; $F = 2.13$

[*] Marketed by: [a] Torrent Pharmaceuticals; [b] Ranbaxy Chemicals; [c] Glaxo SmithKline Pharmaceuticals Ltd. and [d] Cadila Pharmaceuticals.

[**] Average of five determinations.

[***] Tabulated at t-value 95% confidence level 2.77. Tabulated F-value at 95% confidence level 6.39.

official method [60]. There is a close agreement between the results obtained by the proposed and official methods as found from the Student's *t*- and *F*-values. The results obtained by the proposed methods also agreed well with the label claims in all instances.

Recovery experiments were carried out by adding known amounts of pure drug to pre-analysed dosage forms with 96–105% recoveries indicating that tablet excipients and injection diluents did not interfere in the methods.

To conclude the proposed titrimetric methods are the first visual titrimetric methods ever developed for RNH, and are superior to the only titrimetric method [16] (pH- metric) previously reported in terms of speed, simplicity, sensitivity and range of determination. The analysis can be completed in less than 10 min. The spectrophotometric methods are also easier to perform and use inexpensive instrument compared to many reported techniques [2–15], and do not require any expensive or toxic reagents or organic solvents. The most striking advantage of the spectrophotometric methods is the sensitivity, which surpasses the sensitivity of most of the previously reported methods. These advantages coupled with reasonable accuracy and precision render the methods suitable for routine quality control.

Acknowledgements

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