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# Determination of Drug Content of Pharmaceuticals Containing Ranitidine by Titrimetry and Spectrophotometry in Non-Aqueous Medium

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**ABSTRACT:** Three simple, rapid, reliable and cost-effective methods based on titrimetry and spectrophotmetry in non-aqueous medium are described for the determination of ranitidine in pharmaceuticals. In titrimetry, the drug dissolved in glacial acetic acid was titrated with acetous perchloric acid with visual and potentiometric end point detection, crystal violet being used as indicator for visual titration. Spectrophotometry involved adding different amounts of the drug to a fixed amount of perchloric acid-crystal violet mixture followed by measurement of absorbance at 570 nm. The absorbance was found to increase linearly with the concentration of the drug and formed the basis for quantification. The titrimetric methods are applicable over 1-15 mg range of ranitidine, and in spectrophotometry, calibration graph was linear from 10 to 70 μg $ml^{-1}$. The apparent molar absorptivity is calculated to be $2.2 \times 10^3$ l $mol^{-1}$ $cm^{-1}$ and the calculated Sandell sensitivity is 161.7 ng $cm^{-2}$. The limits of detection and quantification are found to be 1.07 and 3.58 μg $ml^{-1}$, respectively. The procedures were used to determine ranitidine in pharmaceutical products and the results were found to be in good agreement with those obtained by the reference method. Associated pharmaceutical materials did not interfere. The accuracy and reliability of the methods were further ascertained by recovery studies via standard-addition technique with percent recoveries in the range 96.3 to 102.5 %.

**KEYWORDS:** Ranitidine, determination, titrimetry, spectrophotometry, non-aqueous medium, formulations.

## INTRODUCTION

Ranitidine, N-(2-{[(5-dimethylamino) methyl]-2-furanyl}-methylthioethyl)-N'-methyl-2-nitro-1, 1' ethane diamine, is the active compound of many pharmaceutical formulations. It competitively inhibits the action of histamine on the $H_2$ receptors of parietal cells, reducing gastric acid secretion under daytime and nocturnal basal conditions and also when stimulated by food, insulin, histamine or pentaglandin. The drug is used for the short-term treatment of active duodenal ulcer and benign gastric ulcer, for the treatment of pathogenic gastrointestinal hypersecretory conditions[1] and to provide short-term symptomatic relief of gastroesophaeal reflux.

Ranitidine (Fig 1) is metabolized in the liver to ranitidine N-oxide, desmethyl ranitidine and ranitidine S-oxide and approximately 70 % of a dose of the drug is excreted in urine as the unchanged drug[2]. The therapeutic importance of this drug has resulted in the development of analytical methods for its determination in biological samples and in pharmaceutical preparations. High performance liquid chromatography (HPLC) is the most widely used technique for the determination of ranitidine in biological samples such as plasma[3-10], serum[11], serum and plasma[12], plasma and urine[13-15], and whole blood and plasma[16]. The technique has also been used for the determination of the drug metabolites[17]. Other techniques like high performance thin layer

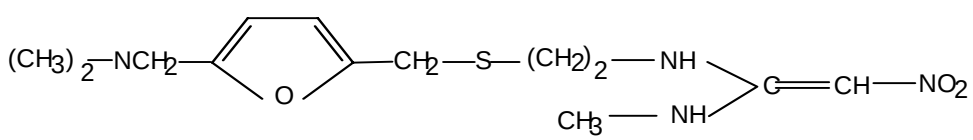


**Fig 1.** Structure of RNH.

chromatography (HPTLC)[18] and differential pulse adsorptive stripping voltammetry[19] have also been applied for the determination of ranitidine in biological samples.

HPLC[20-26] continues to occupy a prominent position among the methods used for the assay of ranitidine in pharmaceutical preparations. Several electroanalytical techniques including polarography[27,28], differential pulse polarography[29], oscillopolarography[30], and linear sweep-voltammetry[31] have been employed for the sensitive determination of ranitidine in pharmaceuticals. Other reported techniques include combined gas chromatography-mass spectroscopy[32], proton magnetic resonance spectroscopy[33], near infrared reflectance spectrophotometry[34], UV spectrophotometry[35-38], automated fluorimetry[39], and capillary electrophoresis[40].

Titrimetric methods with potentiometric[41] and coulometric[42] end-point detection are applicable for 300 mg and 5-90 mg of ranitidine, respectively. Potentiometric methods based on ion-selective electrodes[43-45] proposed by various workers, although applicable in μM to mM concentration range, require strict pH control for accurate and precise results.

Visible spectrophotometry because of its simplicity, sensitivity, speed and reliability is next only to HPLC in terms of its application to the analysis of ranitidine in pharmaceuticals. Methods based on redox[46-48], oxidative coupling[49], nitrosation[50], charge-transfer complexation[51,52] and ion-pair complexation[53,54] reactions have been proposed for the assay of ranitidine in its dosage forms. Hassan and Belal[55] have recently developed a kinetic spectrophotometric method for ranitidine. Procedures based on redox, oxidative coupling and ion-pair complexation reactions, although sensitive, involved unstable reagents[46], a contact time of 30 min[49] or extraction step[53,54], besides lacking in selectivity[46-48]. Methods based on nitrosation[50] reaction is least sensitive (0.3-12 μg $ml^{-1}$) and even the charge-transfer complexation methods are not sufficiently sensitive (50-250 μg $ml^{-1}$). The only titrimetric method based on neutralization reaction[41] in aqueous medium is applicable for 300 mg of drug.

The methods based on modern instrumental techniques[19-39] although sensitive require expensive instrument and maintenance. The present paper describes three methods based on the basic property of the drug molecule. In the titrimetric procedures, the drug solution in glacial acetic acid is titrated directly with acetous perchloric acid, the end point being determined either visually using crystal violet indicator or potentiometrically using modified glass-saturated calomel electrode system. Spectrophotometry involves treating a fixed amount of perchloric acid-crystal violet mixture with the drug and measuring the absorbance at 570 nm. The increase in absorbance is related to the drug concentration. The methods, in addition to being rapid, sensitive, accurate and precise, gave satisfactory results when applied to formulations containing ranitidine. Additionally, the methods can be used in laboratories where modern and expensive instruments such as GC-MS, HPLC, capillary electrophoresis, voltammetry etc, are not available.

## Materials and Methods

### Apparatus

All absorbance measurements were made with a Systronics Model 106 spectrophotometer provided with matched 1-cm quartz cells. Potentiometric titration was performed with an Elico 120 digital pH meter provided with a combined glass-SCE system. The KCl of the salt bridge was replaced with 0.1 M lithium perchlorate in glacial acetic acid.

### Reagents and Solutions

All chemicals used were of analytical reagent grade. All solutions were made in glacial acetic acid unless specified otherwise.

**Perchloric Acid (0.01 M):** To 4.5 ml of 70 % perchloric acid (S.d. Fine Chem., Mumbai, India) was added 150 ml of glacial acetic acid, mixed well; added 10.5 ml of acetic anhydride and allowed the solution to cool for 30 min; finally diluted to 500 ml with glacial acetic acid and allowed to stand overnight. This perchloric acid (~0.1 M) was diluted to 0.01 M with glacial acetic acid and standardized with pure potassium biphthalate and crystal violet indicator.

**Crystal Violet Indicator:** Prepared by dissolving 0.1 g of dye (S.d. Fine Chem., Mumbai, India) in 100 ml glacial acetic acid.

**Perchloric Acid-Crystal Violet Mixture (1.5 mM $HClO_4$ - 0.25 mM Crystal Violet):** Prepared by mixing 15 ml of 0.01 M perchloric acid and 10 ml of 1000 μg $ml^{-1}$ crystal violet solutions and diluting to 100 ml with glacial acetic acid in a drug calibrated flask.

### Standard Drug Solution

Pharmaceutical grade ranitidine hydrochloride (RNH) was procured from Glaxo Smithkline, Nashik, India, as a gift, and was used as received. A stock standard solution containing 2 mg $ml^{-1}$ RNH was prepared by dissolving 500 mg of pure drug in glacial acetic acid and diluting to the mark in a 250 ml calibrated flask. This solution (2 mg $ml^{-1}$) was used for titrimetric work, and for spectrophotometric work, the same was diluted appropriately with glacial acetic acid to get 100

μg $ml^{-1}$ working concentration.

### General Procedures

**Visual Titration (Method A):** A 10 ml aliquot of the drug solution containing 1-15 mg of RNH was pipetted out into a clean and dry 100 ml titration flask, 2 drops of crystal violet indicator was added and titrated with standard 0.01 M perchloric acid to an emerald green end point. The amount of the drug in the measured aliquot was calculated from:

Amount (mg) = VMR

where V = volume of perchloric acid required, ml
M= relative molecular mass of drug,
R = molarity of perchloric acid.

**Potentiometric Titration (Method B):** A 10 ml aliquot of the standard drug solution equivalent to 1-15 mg of RNH was pipetted out into a clean and dry 100 ml beaker and the solution was diluted to 30 ml by adding glacial acetic acid. The combined glass-SCE (modified) system was dipped in the solution. The contents were stirred magnetically and the titrant (0.01M $HClO_4$) was added from a micro burette. Near the equivalence point, the titrant was added in 0.2 ml increments. After each addition of titrant, the solution was stirred magnetically for 30 s and the steady potential was noted. The addition of titrant was continued until there was no significant change in potential on further addition of titrant. The equivalence point was determined by applying the graphical method. The amount of the drug in the measured aliquot was calculated as described under visual titration.

**Spectrophotometric Method (Method C):** Different aliquots (1.0 -7.0 ml) of standard 100 μg $ml^{-1}$ drug solution were accurately transferred into a series of 10 ml calibrated flasks. An exactly measured volume of (2 ml) perchloric acid-crystal violet mixture was added to each flask, and the volume was diluted to the mark with glacial acetic acid, and mixed well. Absorbance was measured at 570 nm against a reagent blank. The increasing absorbance values at 570 nm were plotted against the concentration of the drug to obtain the calibration graph. The concentration of the unknown was read from the calibration graph or calculated from the regression equation obtained from Beer's law data.

### Procedure for Formulations

Ranitin (Torrent Pharmaceuticals, Batch No C112, Expiry date Nov 2005), Histac (Ranbaxy Chemicals, Batch No P1535, Expiry date June 2005), Zinetac (Glaxo SmithKline Pharmaceuticals Ltd., Batch No G302, Expiry date July 2005), Aciloc (Cadila Pharmaceuticals, Batch No N551, Expiry date Feb 2006) - all tablets, Ranitin (Torrent Pharmaceuticals, Batch No C118, Expiry date Nov 2005), Histac (Ranbaxy Chemicals, Batch No P 183, Expiry date June 2005), RNH (Glaxo SmithKline Pharmaceuticals Ltd., Batch No G 960, Expiry date July 2005), Aciloc (Cadila Pharmaceuticals, Batch No N535, Expiry date Feb 2006) - all injections were used in the investigation.

**Tablets:** Twenty tablets were weighed and ground into a fine powder. An amount of powder equivalent to 200 mg of RNH was weighed accurately into 100 ml calibrated flask, 70 ml of glacial acetic acid added and shaken for about 20 min. Then, the volume was made up to the mark with glacial acetic acid, mixed well and filtered using Whatmann No 42 filter paper. The first 10 ml portion of the filtrate was discarded. A suitable aliquot was next subjected to analysis by titrimetry. The filtrate (equivalent to 2 mg $ml^{-1}$) was diluted appropriately to obtain 100 μg $ml^{-1}$ solution and analysed by spectrophotometry using the general procedure described earlier.

**Injections:** The contents of 20 ampoules (each containing 25 mg of RNH) were mixed and an accurately measured volume equivalent to 200 mg of RNH was transferred into 100 ml separatory funnel. Ten ml of 6 M ammonia solution was added and the solution was extracted with three 10 ml portions of chloroform. The chloroform extracts were combined and evaporated to dryness. The residue was dissolved in 50 ml glacial acetic acid and transferred into a 100 ml calibrated flask. The volume was made up to the mark with the same solvent. The solution (2 mg $ml^{-1}$) was subjected to analysis by titrimetry and spectrophotometry as described above after appropriate dilution.

## Results and Discussion

The present methods are based on the neutralization reaction involving the basic property of RNH and employ two techniques. The methods are based on the principle that substances, which are weakly basic in aqueous medium, exhibit enhanced basicity in non-aqueous media thus allowing their easy determination. In the present titrimetric methods, the weakly basic property of RNH was enhanced due to the non-leveling effect of glacial acetic acid and titrated with perchloric acid with visual and potentiometric end point detection. Crystal violet gave highly satisfactory end point for the concentrations of analyte and titrant employed. A steep rise in the potential was observed at the equivalence point with potentiometric end point detection (Fig 2). The Gran's plot (Fig 3) method was applied to ascertain the equivalence point. With both methods of equivalence point detection, a

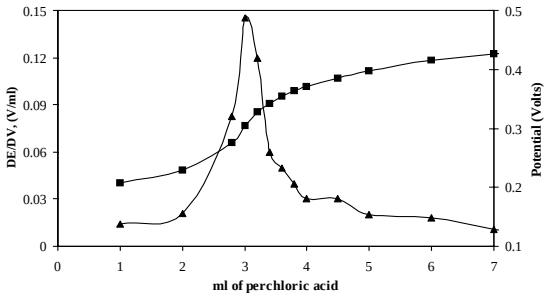


**Fig 2.** Potentiometric end point.

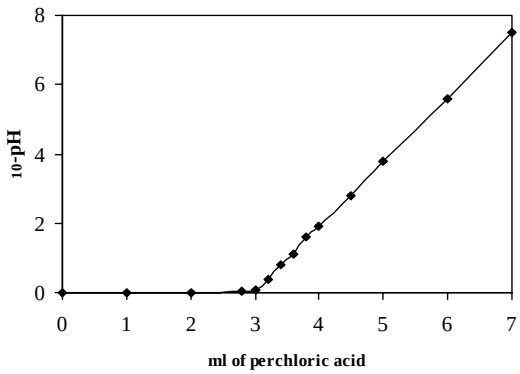


**Fig 3.** Gran's plot.

reaction stoichiometry of 1:1 (drug:titrant) was obtained which served as the basis for calculation. Using 0.01 M perchloric acid, 1-15 mg of RNH was conveniently determined. The relationship between the drug amount and the titration end point was examined. The linearity between two parameters is apparent from the correlation coefficients of 0.9893 and 0.9980 obtained by the method of least squares for visual and potentiometric methods, respectively. From this, it is implied that the reaction between RNH and perchloric acid proceeds stoichiometrically in the ratio 1:1 in the range studied.

Crystal violet (C.I. Basic violet 3) is a dye exhibiting violet colour in the base form and emerald green in the acid form. The spectrophotometric method is based on the facts that the colour of the dye is dependent on the pH of the solution and that the colour change is not sudden but occurs continuously as the pH changes over a definite range. To a fixed amount of acid-dye mixture where the dye is in the acid form (emerald green), different amounts RNH were added. This caused a progressive increase in pH of the solution because of neutralization of acid by the added drug (base), and as a result, the concentration of the base form of the dye increases. This is shown by the proportional increase in the absorbance of the solution at 570 nm (Fig 4) which is corroborated by the correlation coefficient of 0.9892.

In a preliminary study, 20 μg ml$^{-1}$ crystal violet in the base form was found to exhibit a convenient absorbance at 570 nm. In the presence of 2 ml of 1.5 mM perchloric acid in a total volume of 10 ml, this absorbance decreased to a constant minimum. Hence, different amounts of drug were treated with a fixed amount of acid-dye mixture i.e., 2 ml of 1.5 mM $HClO_4$ - 0.25 mM crystal violet (100 μg ml$^{-1}$ of crystal violet) to determine the concentration range of the drug that could be determined by the method of absorbance transitions of the dye accompanying the pH changes. The dye colour even in the presence of drug was found to be stable for several hours, and the order of addition of reactants was not critical.

The increasing absorbance values at 570 nm were plotted against the increasing concentration of drug to obtain a calibration graph. Beer's law is obeyed over the concentration range 10-70 μg ml$^{-1}$, the equation of the line being

$A = - 0.02 + 0.007\ C$

where A is absorbance and C is concentration in μg ml$^{-1}$. The correlation coefficient of the calibration plot was calculated to be 0.9892 (n=7) confirming a linear increase in absorbance with increasing concentration of RNH. The calculated molar absorptivity was found to be 2.2 x 10$^3$ l mol$^{-1}$ ml$^{-1}$ at 570 nm and the Sandell sensitivity was 161.7 ng cm$^{-2}$. The limits of detection and quantification were calculated from the standard deviation of the absorbance measurements obtained from a series of seven blank solutions. The limits of detection and quantification established according to IUPAC definitions[56] were 1.07 and 3.58 μg ml$^{-1}$, respectively.

## Accuracy and Precision

The accuracy and precision of the methods were established by analyzing the pure drug solution at three

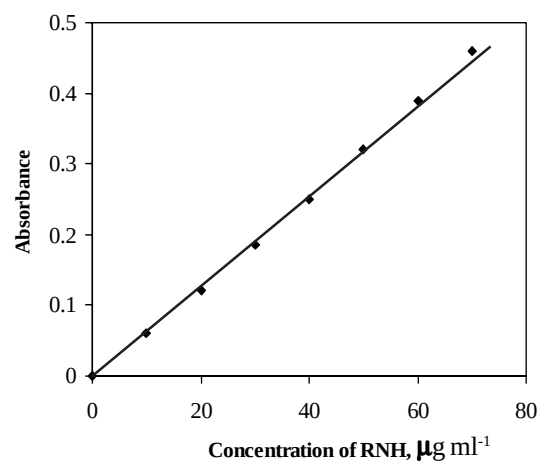


**Fig 4.** Calibration curve.

**Table 1.** Evaluation of Accuracy and Precision of the pure drug.

| Method A* | | | | Method B** | | | | Method C* | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| Amount taken, mg | Amount found, mg | Relative error, % | RSD, % | Amount taken, mg | Amount found, mg | Relative error, % | RSD, % | Conc. taken, μg ml$^{-1}$ | Conc. found, μg ml$^{-1}$ | Relative error, % | RSD, % |
| 3.00 | 3.02 | 0.67 | 1.31 | 3.00 | 3.03 | 0.98 | 0.85 | 20.00 | 19.87 | 0.65 | 1.24 |
| 8.00 | 7.92 | 1.00 | 0.91 | 8.00 | 8.10 | 1.25 | 1.10 | 40.00 | 39.82 | 0.45 | 1.11 |
| 13.00 | 12.94 | 0.46 | 0.08 | 13.00 | 12.84 | 1.23 | 0.79 | 60.00 | 58.84 | 1.93 | 0.92 |

* Average value of seven trials.
** Average value of three trials.
RSD – Relative standard deviation.

different levels. The relative error (%) which is a measure of accuracy, is < 2% revealing high accuracy of the methods. The relative standard deviation (RSD), which is an indicator of precision, is less than 1.5 % and speaks of excellent precision of the methods. The results of the study are compiled in Table 1.

## Application

The proposed methods were successfully applied to determine RNH in tablets and injections. The same batch tablets and injections were analysed by an established procedure[35] for comparison. The results obtained by the proposed methods agree well with those of reference the method[35] and with the label claim.

The results were also compared statistically by a Student's t-test for accuracy and by a variance ratio F-test for precision with those of the reference method at 95 % confidence level as summarized in Table 2. The results showed that the calculated t- and F- values did not exceed the tabulated values inferring that proposed methods are as accurate and precise as the reference method.

Accuracy and reliability of the methods were further ascertained by performing recovery experiments. To a fixed amount of the drug in formulation (pre-analysed), pure drug at three different levels was added, and the total was found by the proposed methods. Each test was repeated three times. The results compiled in Table 3 show that the recoveries were in the range 96.30 - 102.50% indicating that commonly added excipients to tablets such as talc, starch, gelatin, sodium alginate, magnesium stearate, calcium gluconate and calcium dihydrogen orthophosphate, did not interfere in the

**Table 2.** 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 ±SD** | | | |
|---|---|---|---|---|---|
| | | Established method | Proposed methods | | |
| | | | Method A | Method B | Method C |
| Ranitin[a] | 300 | 98.86 ± 0.91 | 99.50 ± 1.25<br>t=0.94; F=1.88 | 98.24± 1.68<br>t=0.65;F=3.40 | 100.36 ± 1.74<br>t=1.41; F=3.66 |
| Histac[b] | 300 | 99.32 ± 1.60 | 100.37 ± 1.26<br>t=1.16; F= 1.61 | 100.42 ± 1.80<br>t=0.88;F=1.26 | 98.63 ± 0.85<br>t=0.89;F=3.54 |
| Zinetac[c] | 150 | 102.28 ± 0.93 | 101.62 ± 1.36<br>t=0.91; F=2.13 | 101.36 ± 0.68<br>t=1.56;F=1.87 | 101.28 ± 1.16<br>t=1.51;F=1.55 |
| Aciloc[d] | 150 | 101.26 ± 0.84 | 100.63 ± 0.71<br>t=1.28; F= 1.40 | 100.69 ± 1.28<br>t=0.73;F=2.32 | 102.28 ± 1.64<br>t=1.30;F=2.47 |
| **Injections** | | | | | |
| Ranitin[a] | 25 | 101.26 ± 0.44 | 101.76 ± 0.62<br>t=1.49; F=1.98 | 100.88 ± 0.74<br>t=0.88;F=2.83 | 101.86 ± 0.85<br>t=1.47;F=3.73 |
| Histac[b] | 25 | 100.48 ± 0.96 | 99.74 ± 1.42<br>t=0.98; F= 2.19 | 100.44 ± 0.78<br>t=0.06;F=1.51 | 99.76 ± 1.28<br>t=1.01;F=1.78 |
| RNH[c] | 25 | 101.38± 1.04 | 102.04± 1.58<br>t=0.70; F=2.31 | 100.86± 0.72<br>t=0.81;F=2.09 | 101.71 ± 0.46<br>t=0.69;F=5.11 |
| Aciloc[d] | 25 | 97.68 ± 0.52 | 98.16 ± 1.22<br>t=0.85; F=3.21 | 98.74 ± 1.08<br>t=1.81;F=4.31 | 98.13 ± 0.66<br>t=1.20;F=1.61 |

* Tabulated t-value at 95 % confidence level 2.77 A & C, 2.37 for method B.
Tabulated F-value at 95 % confidence level 6.39 A & C, 9.28 for method B.
**Average of five determinations in methods A and C, and three determinations in method B.

**Table 3.** Results of recovery study using standard-addition method.

| Dosage form studied | Method A | | | | Method B | | | | Method C | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Amount of drug in extract, mg | Amount of pure drug added, mg | Total found, mg | Recovery of pure drug added, % | Amount of drug in extract, mg | Amount of pure drug added, mg | Total found, mg | Recovery of pure drug added, % | Amount of drug in extract, µg | Amount of pure drug added, µg | Total found, µg | Recovery of pure drug added, % |
| Ranitin 150mg tablets | 5.01 | 6.0 | 11.07 | 101.00 | 4.86 | 6.0 | 10.90 | 100.75 | 101.4 | 200.0 | 304.6 | 101.60 |
| | 5.01 | 7.0 | 11.86 | 97.86 | 4.86 | 7.0 | 11.85 | 99.86 | 101.4 | 300.0 | 399.0 | 99.20 |
| | 5.01 | 8.0 | 13.05 | 100.50 | 4.86 | 8.0 | 12.80 | 99.25 | 101.4 | 400.0 | 511.8 | 102.60 |
| Zinetac 300mg tablets | 5.07 | 6.0 | 11.00 | 98.83 | 5.12 | 6.0 | 11.24 | 102.00 | 98.6 | 200.0 | 296.4 | 98.90 |
| | 5.07 | 7.0 | 12.21 | 102.00 | 5.12 | 7.0 | 12.17 | 100.71 | 98.6 | 300.0 | 401.9 | 101.10 |
| | 5.07 | 8.0 | 12.94 | 98.37 | 5.12 | 8.0 | 13.08 | 99.25 | 98.6 | 400.0 | 498.6 | 100.00 |
| Histac 25 mg Injections | 4.99 | 6.0 | 11.01 | 100.25 | 5.02 | 6.0 | 11.17 | 102.50 | 101.8 | 200.0 | 294.2 | 96.20 |
| | 4.99 | 7.0 | 12.07 | 101.17 | 5.02 | 7.0 | 12.08 | 100.85 | 101.8 | 300.0 | 399.4 | 99.21 |
| | 4.99 | 8.0 | 12.91 | 99.00 | 5.02 | 8.0 | 13.05 | 100.38 | 101.8 | 400.0 | 491.8 | 97.50 |

* Mean value of three determinations.

determination.

## Conclusions

Although HPLC methods with uv-dtection are routinely used for the determination of ranitidine[19-25] the procedures require maintenance of elevated column temperature[19], lack of sensitivity[20,22,23], involve multi extraction steps[21] and also several clean-up steps. They are time-consuming and often poorly reproducible. In contrast, the proposed methods are rapid, simple, precise and accurate. The proposed spectrophotometric method is comparable in sensitivity to many of the existing methods and is superior to many HPLC procedures. The procedure is free from tedious steps like extraction or heating and involves least number of experiment variables, which is reflected in high precision. An additional advantage of the methods is their specificity. Since basic nitrogen is the reaction site, the methods are specific to RNH since none of the excipients normally used in dosage forms contains basic nitrogen. All the three methods are applicable over long dynamic concentration ranges and can serve as useful reference methods, which could be used for routine RNH assay.

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