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Spectrophotometric Determination of Ranitidine Hydrochloride Based on the Reaction with *p*-Dimethylaminobenzaldehyde

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Abstract

A simple and sensitive spectrophotometric method is described for the determination of ranitidine hydrochloride (RNH) in pharmaceuticals. It is based on the formation of colored condensation product with *p*-dimethylaminobenzaldehyde (PDAB) followed by measurement of absorbance at 503 nm. The absorbance was found to increase linearly with the concentration of the drug and formed the basis for quantification. The calibration graph was linear from 50.00 to 350.00 µg mL^{-1}. The apparent molar absorptivity is calculated to be 0.311×10^4 L $mol^{-1}cm^{-1}$and the calculated sandell's sensitivity is 0.1132 µg cm^{-2}. The limits of detection and quantification are found to be 0.00346 and 0.0105 µg mL^{-1} respectively. The procedure is used to determine ranitidine hydrochloride in pharmaceutical products. The associated pharmaceutical materials did not interfere.

Keywords:

Ranitidine hydrochloride, *p*-Dimethylaminobenzaldehyde, Spectrophotometry

1. Introduction

Ranitidine hydrochloride (RNH), chemically N, N dimethyl-5-[2-(1-methylamine-2-nitrovinyl)-ethylthiomethyl]furfurylamine hydrochloride 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]. It acts by blocking histamine receptors which are present on the cells in the stomach lining. Ranitidine binds to H_2 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. As a result, 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.

Several methods have been reported for the determination of ranitidine in bulk, pharmaceutical dosage forms, and/or biological fluids. These methods include kinetic spectrophotometry [2, 3], HPLC [4-8], coulometry [9], capillary electrophoresis [10, 11], fluorimetry [12], HPTLC [13], voltammetry [14], potentiometry [15] and polarography [16]. 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. There are several reports of the determination of RNH by spectrophotometry involving the use of Folin-Ciocalteu reagent [17], N-bromosuccinimide

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[18], Cerium (IV) [19], 3-methyl-2-benzothiazoline hydrazone-iron (III) [20], 7, 7, 8, 8 tetracyanoquinodimethane [21], 2, 6- dichloroquinone chlorimide [22], bromothymol blue [23], potassium dichromate [24], perchloric acid [25], DDQ [26], $Hg(SCN)_2$ [27]. These methods are based on redox, coupling, charge-transfer complexation, and ion pair complexation reactions. Already reported spectrophotometric methods suffer from one or other deficiency such as heating or extraction step, critical dependence on acid/pH condition, use of non-aqueous medium/expensive chemicals, poor sensitivity and/or narrow range of linear response.

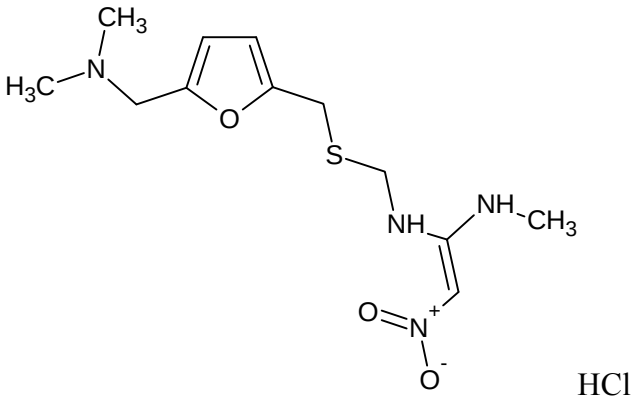


Fig 1. Structural formula of ranitidine hydrochloride

The present investigation is based on the condensation of RNH with *p*-dimethylaminobenzaldehyde (PDAB). The method aims to develop sensitive and cost effective method for the determination of RNH in pure form and in tablets by spectrophotometry.

2. Experimental

2.1. Apparatus

UV-1601 PC (Shimadzu, Japan) UV Spectrophotometer with matched 1-cm quartz cells were used for all measurements.

2.2. Materials and reagents

All chemicals used were of analytical reagent grade. *p*-Dimethylamino-benzaldehyde (Central Drug House Ltd., India 99.0 % pure) solution of 0.025N was prepared in 2N Hydrochloric acid. Ranitidine hydrochloride (Orchev Pharma Ltd., India 99.71% pure) was obtained and used as such. A standard stock solution containing 1000 µg mL^{-1} RNH was prepared by dissolving 100 mg of pure drug in water and diluting to the mark in a 100 mL calibrated flask.

2.3. Procedure

Aliquots containing 50.00-350.00 µg mL^{-1} RNH were transferred into a series of 10 mL standard flasks by means of a micro burette. To each flask 3 mL of 0.025N *p*-Dimethylaminobenzaldehyde was added and kept aside for 20 min for color development. It was then diluted up to the mark with distilled water. The absorbance was measured against the reagent blank at 503 nm. The absorption spectrum of the PDAB-RNH condensation product (a) and corresponding reagent blank (b) is shown in Fig. 2. The increase in absorbance was plotted against the RNH concentration.

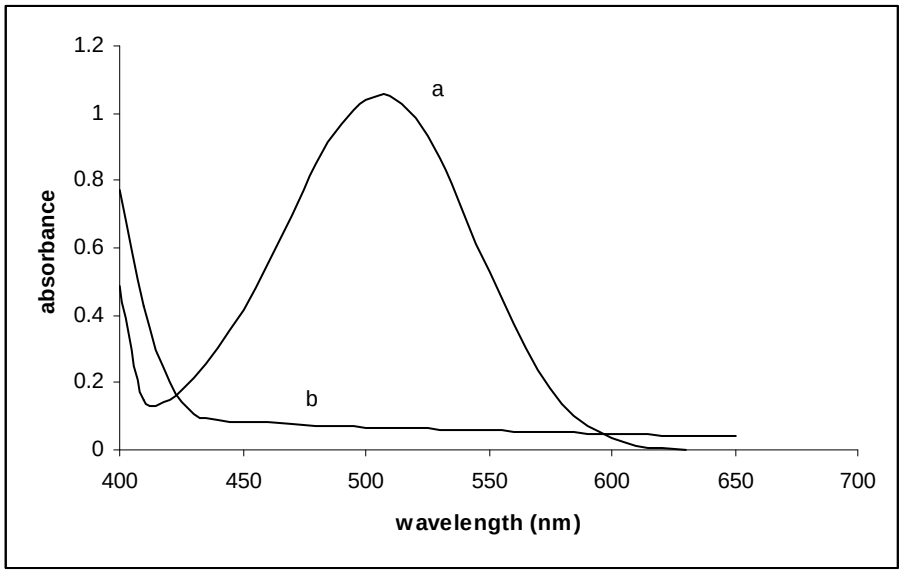


Fig. 2. (a) The absorption spectrum of the PDAB-RNH condensation product (b) corresponding reagent blank.

2.4. Stoichiometric relationship

The mole ratio method [28] employed a 0.01 mol L^{-1} solution of both the drug and the reagent under consideration (PDAB) to determine the stoichiometry of PDAB- RNH mixture. In this method a series of solutions was prepared in which the concentration of RNH is kept constant and that of the PDAB is varied. The absorbance of the solutions are measured at 503 nm and plotted versus the ratio of the variable.

2.5. Procedure for tablet formulations

Rantac -168 mg (Unique's pharmaceuticals Ltd., India), Zinetac -168 mg (Glaxo Smithkline Pharmaceuticals Ltd., India) tablets were used in the investigation. Three tablets were taken and ground into a fine powder. Powder equivalent to 168 mg of RNH was weighed into a 100 mL calibrated flask, 60 mL of water was added and shaken well and filtered. First 10 mL portion of the filtrate was discarded. A suitable aliquot was next subjected to analysis by using the procedure described above.

3. Results and Discussions

The method is based on the condensation of RNH with PDAB to form a red colored product (Scheme 1). The absorbance of the colored product measured is a quantitative measure of the concentration of RNH. Constant absorbance values were obtained with 3 mL of 0.025 N PDAB. The stability of the product was tested by measuring the absorption spectra as soon as the product formed [Fig. 3 (a)] and after 10 hrs [Fig. 3 (b)]. The absorbance was found to be the same both the times. A comparison of the reported methods and the proposed method is given in Table 1.

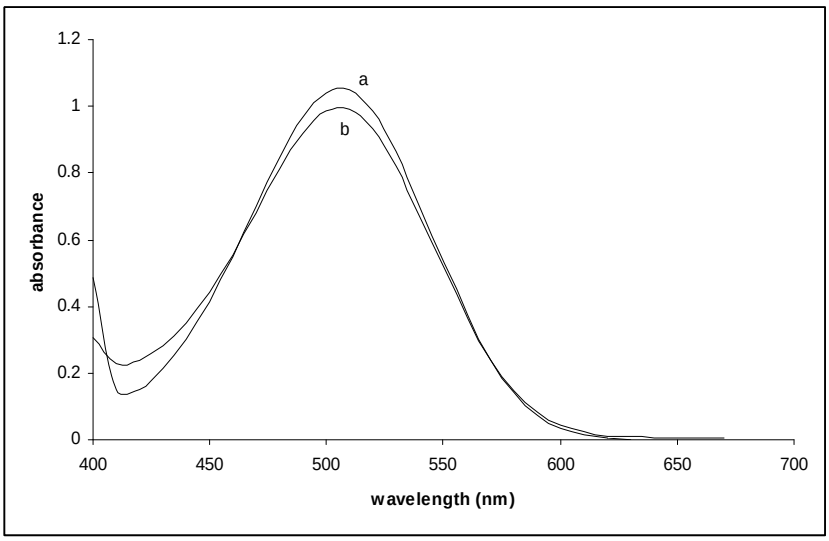
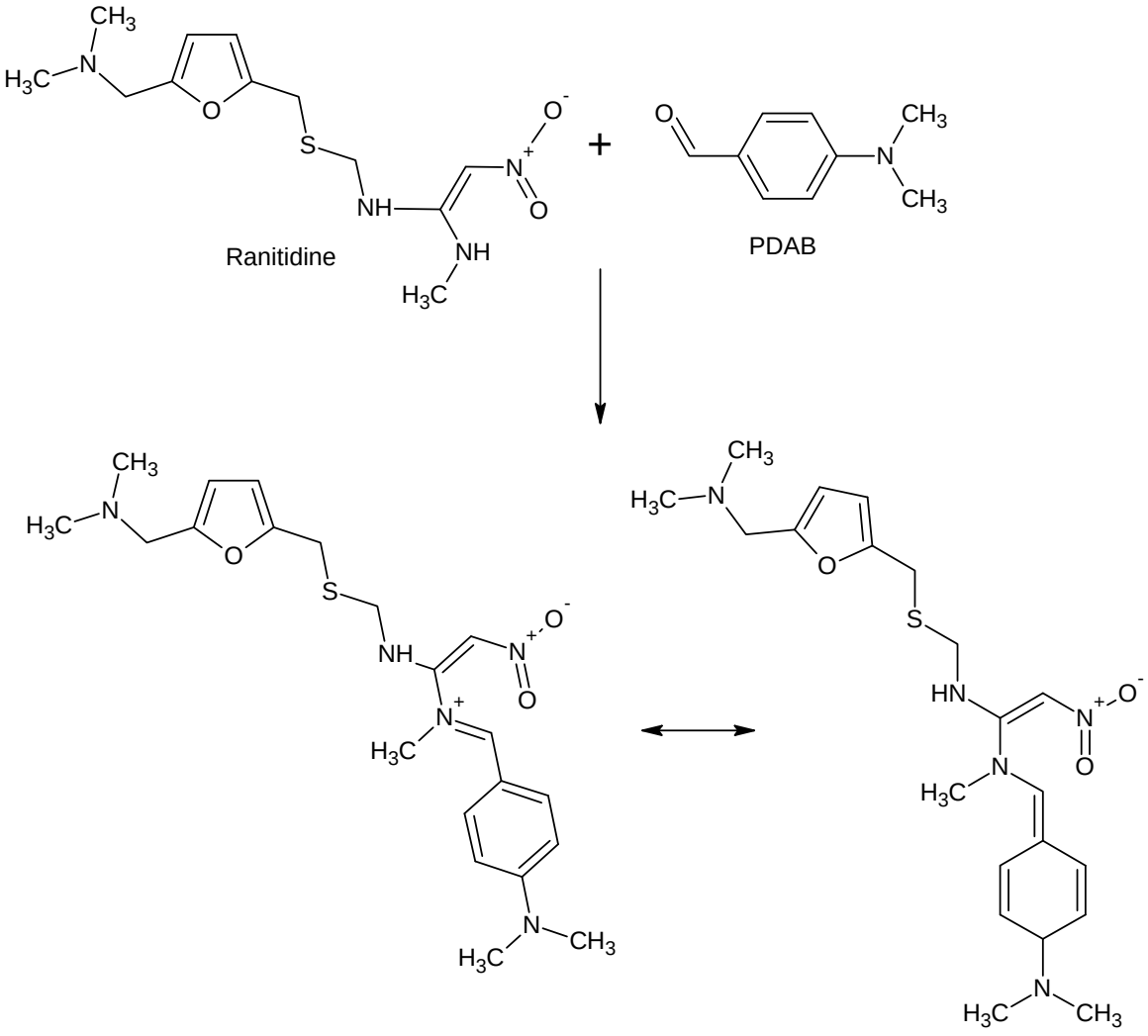


Fig. 3. (a) The absorption spectrum as soon as the product formed (b) absorption spectrum of the product after 10 hrs.



Scheme 1. Condensation reaction of RNH with PDAB

3.1. Effect of reagent concentration

PDAB (0.025 N) is used as coupling agent for the reaction. The increase in the absorbance was tested by adding different volumes of the reagent (0.5 mL, 1.0 mL, 3.0 mL). It was observed that 3.0 mL of PDAB showed maximum absorbance for the reaction.

3.2. Effect of acid concentration

The reaction was carried out in acid medium. Preliminary experiments were performed to fix the initial concentration of HCl. 2 mol L^{-1} HCl was sufficient for maximum color intensity.

3.3. Effect of temperature and time

The reaction was carried out at room temperature (27 ± 4˚C). The increase in the temperature did not have any effect on the absorbance. The absorbance was studied at different time intervals. It was observed that the reaction mixture showed maximum absorbance at 20 min.

3.4. Molar ratio

The plot obtained by the molar ratio method indicated that PDAB and RNH form condensation product in a molar ratio of 1:1 (Fig. 4).

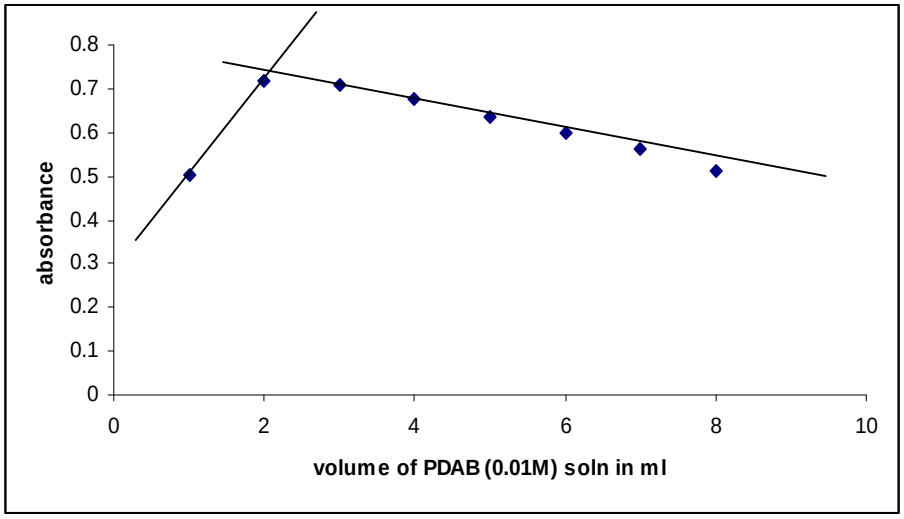


Fig. 4. Mole-ratio method to determine the stoichiometric relationship between PDAB and RNH

3.1. Analytical Data

A linear correlation was found between absorbance at λ_{max} and concentration ranges given in Table 2. Sensitivity parameters such as molar absorptivity, sandell's sensitivity, detection limit and quantification limit are presented in Table 2. The limits of detection (LOD) and quantification (LOQ) were calculated according to the current ICH guidelines [29] using the following formulae:

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

Where σ is the standard deviation of reagent blank and S is the slope of the calibration curve. Regression analysis of Beer's law data using the method of least squares was made to evaluate the slope (b), intercept (a), correlation coefficient (R) and is also given in Table 2.

Table 1. Comparison table for the proposed method and reported method.

S.No.	Reagents Used	Linear range (μg mL^{-1})	Remarks	Reference
1.	F-C reagent	40.00-240.00	Least sensitive	[17]
2.	$KMnO_4$-NBS/dyes	5.00-30.00 (5.2×10^3) 0.50-4.00 (1.89×10^4) 0.40-2.80 (4.2×10^4) 0.40-2.80 (7.2×10^4)	"	[18]
3.	Cerium(IV)/ a) Chromotrope 2R b) Rhodamine 6G	0.1-2.8 (1.91×10^5) 0.1-2.6 (1.74×10^5)	Involves boiling	[19]
4.	Iron (II)- MBTH	5.00-18.00	Uses an expensive reagent	[20]
5.	TCQD	1.00-6.00	Requires heating at 70˚C	[21]
6.	DCBC	10.00-50.00	Involves boiling for 20 min.	[22]
7.	Bromothymol blue strict	1.00-20.00	Involves extraction & pH control	[23]
8.	$KCrO_3$ / a) Diphenylcarbazide b) Fe(III)-SCN methods c) Fe(III)& 1,10-Phenanthroline	 5.00-50.00 5.00-80.00 10.00-100.00	 Indirect	[24]
9.	Perchloric acid-medium crystal violet	10.00-70.00	Requires non-aqueous	[25]
10.	a) DDQ b) p- Chloranilic acid	20.00-140.00 (2.431×10^3) 20.00-240.00 (1.052×10^3)	Less sensitive	[26]
11.	Hg $(SCN)_2$- Iron (III)	5.00-70.00 (3.27×10^3)	Less sensitive	[27]
12.	PDAB	50.00-350.00 (0.3114×10^4)	Applicable to wide range	Present method

F-C: Folin-Ciocateau; NBS: N-Bromosuccinimde; MBTH: 3-Methyl-2-benzothiazolinone hydrazone; TCQD: Tetracyanoquinodimethane; DCBC: Dichloro-p-benzoquinone chlorimide; DDQ: 2, 3 dichloro-5, 6-dicyanoquinone.

Table 2. Analytical Parameters

λmax nm	503
Beer's Law limit (μg mL^{-1})	50.00-350.00
Molar Absorptivity ($Lmol^{-1}cm^{-1}$)	0.3114×10^4
Sandell's Sensitivity (μg cm^{-2})	0.1132
Limit of Detection **(μg mL^{-1})	0.0034
Limit of Quantification **(μg mL^{-1})	0.0105
Regression Equation *	Y=a+ bX
Slope (b)	0.8145
Intercept (a)	0.1147
Correlation coefficient (R)	0.9972

* Y is the absorbance and X concentration in μg mL^{-1}

* * Calculated according to ICH guidelines.

3.2. Accuracy and Precision

The accuracy and precision of the method was established by analyzing the pure drug solution at 5 different levels (within working limits). The relative error (%) which is a measure of accuracy & RSD (%) a measure of precision are summarized in Table 3 and reveal the high accuracy and precision of the method.

Table 3: Evaluation of Accuracy and Precision.

Amount taken(µg mL^{-1})	*Amount found(µg mL^{-1})	RE (%)	SD (µg mL^{-1})	RSD (%)
100.0	100.80	0.80	0.109	1.086
150.0	149.00	0.60	0.115	0.775
200.0	201.60	0.80	0.261	1.293
250.0	252.40	0.96	0.261	1.032
300.0	301.20	0.40	0.109	0.364

*Mean value of five determinations
RE-Relative error; SD-Standard Deviations; RSD-Relative Standard Deviation.

3.3. Interference Study

In pharmaceutical analysis, it is important to test the selectivity towards the excipients added to the pharmaceutical preparations. Commonly encountered excipients such as glucose, starch, talc did not interfere in the determination of RNH.

3.4. Applications

The proposed method was successfully applied to determine RNH in tablets. The content of the tablet formulation was calculated by applying suitable dilution factor. The results for the tablets were compared statistically with those of the tabulated value at 95% confidence level. The calculated student's t-test did not exceed the tabulated value. Table 4 gives the results of the determination from which it is clear that there is close agreement between the results obtained by the proposed methods and label claim.

Table 4: Results of Determination of RNH in Tablets

Brand Name	Labelled Amount(mg)	% Found* ±SD	t-test
Rantac[a]	168 mg	99.04±0.192	1.57
Zinetac[b]	168 mg	100±0.252	0.39

* Mean of 5 determinations
a Unique's pharmaceuticals
b Glaxo Smithkline Pharmaceuticals Ltd.
Tabulated t-value at 95% confidence level is 2.77.

4. Conclusion

Simple and rapid determination of RNH has been developed. The method is easy to perform and do not contain any stringent experimental variables which effect the reliability of

the results. All the analytical reagents used are inexpensive, have good shelf life and are available in any analytical laboratory. There is no interference from common additives and excipients. The method thus can be used in the determination of RNH in pure and dosage forms.

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