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Method development, validation and dissolution studies of ranitidine in its pharmaceutical dosage under different conditions by spectrophotometry

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ABSTRACT

Ranitidine is a common drug used as antacid. In the present study, method (under International Conference of harmonization (ICH) Guidelines) for the validation of Ranitidine in its formulation (Zantac 300mg), was developed spectrophotometrically at λ_{max} *= 314 nm. The medium of dissolution was water, at* 30^0C *and* 37^0C*. The concentration of the drug from 1 to 35 ppm was prepared and the regression of the curve was Y = 0.031x − 0.014,* $R^2 = 999$*.The percentage of relative standard deviation (RSD) 75.3, limit of detection (LOD) 0.47, limit of quantization (LOQ) 1.57. Method detection limit (MDL) value 0.47 (t-value 1.56) was determined. The calculated values of Sandells sensitivity and the molar absorptivity were 0.00301384* $\mu g / ml / cm^2$ *and* $4.4\times10^6 M^{-1}cm^{-1}$ *respectively. The average recovery of the solution (average of two results of recovery) was made to 99.82%. The label claim was made from the average of two verification test as 100. The solution was stable up to 24 hours, and other analytical parameters were also verified simultaneously.*

Key words: Ranitidine, Dissolution, Validation, International Conference of harmonization (ICH), Spectrophotometrically.

INTRODUCTION

Ranitidine is H^+ antagonist receptor, widely used for duodenal ulcer that inhibits stomach acid production [1]. Chemically it is N – [2-[(5-dimethyl amino – methyl) Furan 2-yl] methyl thio] ethyl] – N- methyl – 2- nitro ethane – 1, 1 – diamine hydrochloride (Fig- 1) (CAS # 71130 – 06-8). Ranitidine can be administered preoperatively to reduce the risk of aspiration pneumonia. Patients with zollinger-ellison syndrome when given with high dosage of Ranitidine were found to cause no harm, as reported in Indian pharmacopeia(IP),British pharmacopeia(BP), & United states pharmacopeia (USP)[2,3,4]. Serum concentration of 36 to94 mg / ml of Ranitidine have been shown to inhibit 50% of stimulated gastric acid secretion [5].

It has been validated using HPLC [6, 7], HTPLC [8], HPLC with Fluorescence [9], UV- Visible spectrophotometry [10-11](Other drugs), pharmacokinetically [12], Liquid chromatography [13], Electrophoresis [14] , Super critical liquid chromatography [15]has been reported. However the main objective of the method developed in the present study is to simplify and validate the experiment. The present method involves validation of the method, which involves two different temperatures and its comparison at different lab, and working conditions, followed by cross verification by dissolution of the drug. The method involved is under the guidelines of, International conference of harmonization (ICH) [16-17] and under the Analytical detection limit guidance [19].

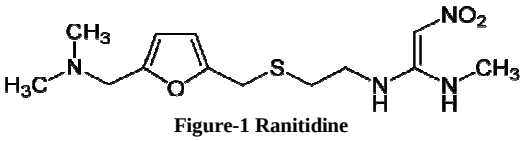

Figure-1 Ranitidine

EXPERIMENTAL SECTION

Materials

20 tablets of 300 mg Zantac tablets (GlaxoSmithKline), standard Ranitidine, potassium dihydrogen phosphate, methanol, NaOH, HCl were of analytical grade.

Instrumentation

A Systronics model 117 UV -Visible spectrophotometer with 1 cm quartz cell, used for absorbance measurements. Sonification chamber and analytical balance (Mattler Toldo B 2048) was used, Whatmann filter Paper No: 41 was used for the filtration of placebo.

Standard solution

0.68 gm of potassium dihydrogen phosphate was dissolved in 100 ml distilled water and sonified. The resulting solution P^H was adjusted to 5.1, with 0.1 N NaOH, and 0.2 M HCl solutions, and is further called as diluent solution. 10 mg of standard Ranitidine (pure sample) was transferred to 20 ml flask and made up with the diluent solution and labeled as 500 $\mu g / ml$ of standard solution of Ranitidine.

Sample preparation/Placebo separation

20 Zantac tablets of 300 mg each were finely powdered and 10 mg of powdered Zantac was transferred to 20 ml flask and was sonified for 10 minutes. Later it was made up by the diluent solution and labeled as 500 $\mu g / ml$ of sample solution. Subsequently 10 different concentrations from 1.0 to 35.0 ppm were prepared for further absorbance recordings.

Determination of λ_{max}

The solutions prepared were scanned between wavelength range of 200 to 400 nm and λ_{max} was found to be 314 nm for the standard solution of ranitidine.

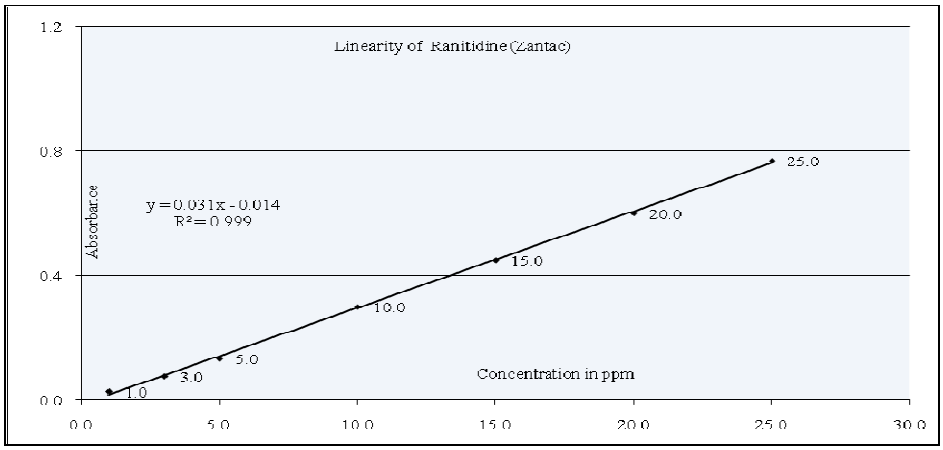

Figure-2 Linearity and range of Ranitidine in its dosage form

Method Involved

The method development involves scanning of standard solution and sample solution of ranitidine at 30^0C and 37^0C at λ_{max} 314nm.The standard solution and sample solution made were subjected to absorbance measurements. The further sequence of experiment was carried out as per the guidelines of ICH and the method is validated accordingly.

Method validation

Linearity and Range

The sample solution of Ranitidine of 10 different concentrations 1, 3, 5, 10, 15, 20, 25, 28, 30 and 35 ppm were subjected to absorbance at 314 nm. The drug obeyed Beer's law as given in Figure - 2. The slope intercept Y = $0.031x - 0.014$ and regression $R^2 = 0.999$ was established from values of absorbance measured (table-1).

Precision

Freshly prepared sample solution of Zantac was further made into six different concentrations. Then each concentration was subjected to absorbance at 314nm. From the absorbance recordings, mean deviation, standard deviation and RSD were calculated as given in table -1. Intermediate precision absorbance recording were also taken by two different analysts on alternate days, and average of both was considered.

Table 1: Data of various parametric values of Ranitidine

PARAMETER	Absorbance		% Mean value		%Standard deviation(SD)		%Relative standard deviation(RSD)	
Linearity (Conc in ppm)	1 (0.036)	20(0.590)	0.50		0.38		75.39	
	3(0.096)	25(0.769)						
	5(0.0187)	28(0.862)						
	10(0.319)	30(0.910)						
	15(0.449)	35(1.044)						
Precision	0.752	-	92.27	-	0.031		3.98	
	0.789	-	96.80	-				
	0.832	-	101.77	-				
	0.824	-	106.97	-				
	0.794	-	97.42 (Avg-98.68	-				
Robustness (At Varying λ_{max})	289 nm	293 nm	289 nm	293 nm	SD at 289nm	SD at 293nm	RSD at 289nm	RSD at 293nm
	0.826	0.819	101.99	101.91	2.89	2.90	2.86	2.88
	0.825	0.818	101.87	101.85				
	0.785	0.777	96.51	96.68				
	0.798	0.791	98.53	98.55				
	0.813	0.805	100.26	100.23				
Robustness (At varying temp) in ^{0}C)	35^0C	39^0C	35^0C	39^0C	SD at 35^0C	SD at 39^0C	RSD at 35^0C	RSD at 39^0C
	0.715	0.794	95.62	101.35	4.4	0.32	4.62	0.31
	0.819	0.791						
	0.757	0.791						
	0.791	0.791						
	0.774	0.787						
Stability of solutions (Time 0,4,8, 24 Hr)	Sp	Sd	Sp	Sd	SD of Sp	SD of Sd	RSD of Sp	RSD of Sd
	0.642	0.743	0.653	0.739	0.007	0.01	1.16	1.46
	0.660	0.723						
	0.655	0.745						
	0.653	0.745						
Recovery	At concentration (ppm)	Abs	-	-	-	-	-	% of Recovery
	25	0.725	0.555		SD- 0.238		%RSD 42.86	99.86
	50	1.430						99.23
	70	1.787						99.47
	85	1.997						99.54
	100	2.340						101.01

**SD= Standard deviation, RSD= Relative standard deviation, Abs=Absorbance, Sp = Sample Solution, Sd = Standard solution.*

Robustness

The absorbance of ranitidine sample solution at varying wavelength and temperature to check the sustainability at change in λ_{max}, P^H and temperature was measured. The temperature of the solution was raised to 35^0C and 39^0C and absorbance was recorded. Later absorbance of freshly prepared sample solution was recorded at varying λ_{max} 289 and 293 nm and given in table-1.

Stability studies

Sample solution of Zantac was freshly prepared and immediately absorbance measurements were made, at 0, 4, 8 and 24 hours interval. In similar mode absorbance measurements were made for standard solution in same time frame as recorded for sample solution (table- 1)

Recovery

Accuracy of the method involved, was cross verified based on recovery studies. By taking 1 ml of standard solution, 500 $\mu g / ml$ and sample solutions, concentrations of 25, 50, 70, 85, and 100 ppm were made and their absorbance were recorded (table-1).

RESULTS AND DISCUSSION

The standard solution and sample solution of Ranitidine scanned has shown of λ_{max} =314nm at 30^0C and 37^0C. This indicates that sample solution and standard solution of Ranitidine can be validated precisely at different temperatures and working condition. To verify this, different concentrations of sample and standard solutions were prepared and scanned for linearity and range. The solutions scanned were found to obey beers law which is mandatory for the process of validation. A plot between concentration and absorbance measured gives a straight line, following the equation, $Y = 0.031x - 0.014$, with a regression of 0.999.The absorbance values obtained at 30^0C and 37^0C were considered as two sets to calculate t-value. The t-value was calculated as 1.56, from which MDL value 0.47 was calculated ($MDL = slope \times t - value$) [19].

Later the standard deviation of the sample solution for precision values 0.031 and the percentage of relative standard deviation (3.98) were calculated. Both the values were found to be within the permitted limits [16-19]. Robustness of the method involved was testified by varying the wavelength, temperature and P^H of the sample solution against standard solution.

Table -2 Absorbance characteristic of Ranitidine

Absorption maxima λ_{max}	314 nm
Beers law limit for the drug sample solution	1-35 (ppm)
Coefficient of correlation	0.99994
Regression equation (absorbance versus concentration)	Y = 0.3000x -0.014
Slope(m)	0.03000
Y –Intercept	0.00358
Molar Absorptivity 1 / (M.Cm)	4.48 x 10^6 ($\mu m.cm$)
Sandells sensitively	0.00301384
LOD ($3s \tan dard\ deviation \div slope$)	0.4
LOQ ($10 \times Slope$)	1.57
MDL value	0.47
t-value	1.56
Lower critical limit(LCL)	0.0192
Upper critical limit(UCL)	1.034
Average absorbance	0.509
Optical density	0.5(length of cell=1cm)
Signal-noise ratio	1.339(accepted)

Table-3 Comparison of the method involved/results

Method	Formulation	Label claim	% label claim found	Standard deviation (SD)	% Recovery ± SD
A (at 30^0C)	Zantac	300 mg	99	0.36	99.8 ± SD
B (at 37^0C)	Zantac	300 mg	101	0.31	101 SD

The stability of the sample solution was measured at different interval of time frame as discussed and the solution was stable up to 24 hours [18]. The solution started degrading at 36^{th} hour and almost degraded at 48^{th} hour. Recovery of the drug was made as per the ICH guidelines [16] and recovery of 101% was made, which indicate the accuracy and simplicity of the method involved. The data presented in tables 2 and 3 summarizes the validation of the method.

CONCLUSION

The validation process is simple, accurate and economical.

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