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METHOD DEVELOPMENT AND VALIDATION FOR THE DETERMENATION OF RANITIDINE IN ITS FIXED DOSE DRUG PRODUCT BY USING RP-HPLC

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ABSTRACT

Method development and validation for the determination of ranitidine init's fixed dose drug product by using RP-HPLC .Chromatogram was run through std symmetry (150x4.6mm,5µm). Mobile phase containing buffer acetonitrile :0.1% OPA : acetonitrile taken in ratio (50:50) was pumped through column at a flow rate 1ml /min. buffer used in this method was 0.1% OPA buffer. Temperature was maintained at ambient temperature (25**°C).** Retention time (RP) of ranitidine was found to be 4.337 mins. Percentage rsd of the ranitidine was found to be 0.4. %recovery of time 100.42 for Ranitidine. Assay was obtained as 100.4% for ranitidine. Regression equation of ranitidine is y=12587x+1366.2. Correlation coefficient R2 0.999 of ranitidine. Retention time was decreased and that run time was decreased. So that method developed was simple and economical.

Keywords: Ranitidine, RP-HPLC, Correlation coefficient, Retention and Chromatogram.

INTRODUCTION

Due to rapid growth of pharmaceutical industry during last several years, number of pharmaceutical formulations are enter as a part of health care system and thus, there has been rapid progress in the field of pharmaceutical analysis. Developing analytical method for newly introduced pharmaceutical formulation is a matter of most importance because drug or drug combination may not be official in any pharmacopoeias and thus, no analytical method for quantification is available. To check the quality standards of the medicine various analytical methods are used. Modern analytical techniques are playing key role in assessing chemical quality standards of medicine. Thus analytical techniques are required for fixing standards of medicines and its regular checking.

- HPLC is probably the most universal type of analytical procedure; its application areas include quality control, process control, forensic analysis, environmental monitoring and clinical testing. In addition HPLC also ranks as one of the most sensitive analytical procedures and is unique in that it easily copes with multi-component mixtures. It has achieved this position as a result of the constant evolution of the equipment used in LC to provide higher and higher efficiencies at faster and faster analysis times with a constant incorporation of new highly selective column packings.

EXPERIMENTAL METHODS
DRUG PROFILE
RANITIDINE
Structure-

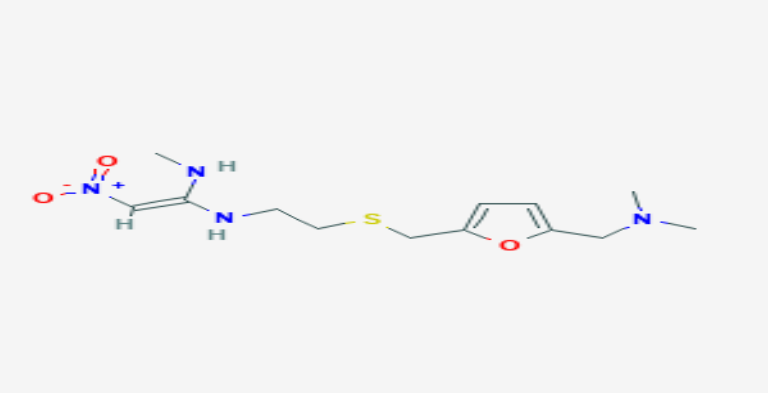

Fig. 1: Structure of Ranitidine

Chemical name
Dimethyl[(5-{[(2-{[(E)-1-(methylamino)-2-nitroethenyl]amino}ethyl)sulfanyl]methyl}furan-2-yl)methyl]amine

Molecular formula- $C_{13}H_{22}N_4O_3S$
Molecular Weight - 314.404

Description
A non-imidazole blocker of those histamine receptors that mediate gastric secretion (H2 receptors). It is used to treat gastrointestinal ulcers.

Mechanism of action
The H2 antagonists are competitive inhibitors of histamine at the parietal cell H2 receptor. They suppress the normal secretion of acid by parietal cells and the meal-stimulated secretion of acid. They accomplish this by two mechanisms: histamine released by ECL cells in the stomach is blocked from binding on parietal cell H2 receptors which stimulate acid secretion, and other substances that promote acid secretion (such as gastrin and acetylcholine) have a reduced effect on parietal cells when the H2 receptors are blocked.

Pharmacodynamics
Ranitidine is a histamine H2-receptor antagonist similar to cimetidine and famotidine. An H2-receptor antagonist, often shortened to H2 antagonist, is a drug used to block the action of histamine on parietal cells in the stomach, decreasing acid production by these cells. These drugs are used in the treatment of dyspepsia, however their use has waned since the advent of the more effective proton pump inhibitors. Like the H1-antihistamines, the H2 antagonists are inverse agonists rather than true receptor antagonists.

Protein binding
15%

Metabolism
Hepatic. Ranitidine is metabolized to the N-oxide, S-oxide, and N-desmethyl metabolites, accounting for approximately 4%, 1%, and 1% of the dose, respectively.

Route of elimination
The principal route of excretion is the urine (active tubular excretion, renal clearance 410mL/min), with approximately 30% of the orally administered dose collected in the urine as unchanged drug in 24 hours.

Half life
2.8 – 3.1 hours.

Affected organisms
Humans and other mammals.

OPTIMIZED CHROMATOGRAPHIC CONDITIONS

Instrument used	:	Waters HPLC with auto sampler and UV detector.
Temperature	:	Ambient
Column	:	YMC ODS (4.6 x 150mm, 5μm)
Buffer	:	0.1% OPA
pH	:	3.0
Mobile phase	:	Acetonitrile: 0.1% OPA (50:50)
Flow rate	:	1 ml per min
Wavelength	:	228 nm
Injection volume	:	20 μl
Run time	:	10 min.

PREPARATION OF BUFFER AND MOBILE PHASE
Preparation of 0.1% OPA buffer
Take 1 ml of OPA in 1000 ml of HPLC water, pH was adjusted with NaOH up to 3.0. Final solution was filtered through 0.45 μ Membrane filter and sonicate it for 10 mins.

Preparation of mobile phase
Accurately measured 500 ml of Acetonitrile (50%) and 500 ml of above buffer (50%) were mixed and degassed in an ultrasonic water bath for 10 minutes and then filtered through 0.45 μ filter under vacuum filtration.

Diluent Preparation
The Mobile phase was used as the diluent.

ASSAY
Standard Solution Preparation
Accurately weigh and transfer 150 mg of Ranitidine working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent. Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Ranitidine)

Sample Solution Preparation
Accurately weigh 10 tablets crush in motor and pestle and transfer equivalent to 150 mg (230 mg of tablet power) of Ranitidine sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Ranitidine)

Procedure
Inject 20 μL of the standard, sample into the chromatographic system and measure the areas for Ranitidine peaks and calculate the %Assay by using the formulae.

VALIDATION PARAMETERS
1. LINEARITY
Preparation of stock solution
Accurately weigh and transfer 150 mg of Ranitidine working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)

Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.

Preparation of Level – I (15 ppm of Ranitidine**)**
1 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent.

Preparation of Level – II (30 ppm of Ranitidine**)**
2 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent.

Preparation of Level – III (45 ppm of Ranitidine**)**
3 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent.

Preparation of Level – IV (60 ppm of Ranitidine**)**
4 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent

Preparation of Level – V (75 ppm of Ranitidine**)**
5 ml of above stock solutions has taken in 10 ml of volumetric flask, dilute up to the mark with diluent

Procedure
Inject each level into the chromatographic system and measure the peak area.
Plot a graph of peak area versus concentration (on X-axis concentration and on Y-axis Peak area) and calculate the correlation coefficient.

Acceptance Criteria
Correlation coefficient should be not less than 0.99.

2. PRECISION
Preparation of stock solution
Accurately weigh and transfer 150 mg of Ranitidine working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Ranitidine)

Procedure
The standard solution was injected for six times and measured the area for all six Injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Acceptance Criteria
The % RSD for the area of six standard injections results should not be more than 2%**.**

3. INTERMEDIATE PRECISION/RUGGEDNESS
To evaluate the intermediate precision (also known as Ruggedness) of the method, Precision was performed on different day.

Preparation of stock solution
Accurately weigh and transfer 150 mg of Ranitidine working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Ranitidine)

Procedure
The standard solution prepared in the precision was injected on the other day, for six times and measured the area for all six injections in HPLC. The %RSD for the area of six replicate injections was found to be within the specified limits.

Acceptance Criteria
The % RSD for the area of six standard injections results should not be more than 2%.

4. ACCURACY
For accuracy determination, three different concentrations were prepared separately i.e. 50%, 100% and 150% for the analyte and chromatograms are recorded for the same.

Preparation of Standard stock solution
Accurately weigh and transfer 150 mg of Ranitidine working standard into a 100 ml clean dry volumetric flask add about 50 ml of diluent and sonicate to dissolve it completely and make volume up to the mark with the same solvent. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Ranitidine)

Preparation Sample solutions
For preparation of 50% solution (With respect to target Assay concentration)
Accurately weigh 10 tablets crush in motor and pestle and transfer equivalent to 75 mg (115 mg of tablet power) of Ranitidine sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (22.5 ppm Ranitidine)

For preparation of 100% solution (With respect to target Assay concentration)
Accurately weigh 10 tablets crush in motor and pestle and transfer equivalent to 150 mg (230 mg of tablet power) of Ranitidine sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (45 ppm Ranitidine)

For preparation of 150% solution (With respect to target Assay concentration)
Accurately weigh 10 tablets crush in motor and pestle and transfer equivalent to 225 mg (345 mg of tablet power) of Ranitidine sample into a 100 ml clean dry volumetric flask add about 50 mL of diluent and sonicate it up to 30 mins to dissolve it completely and make volume up to the mark with the same solvent. Then it is filtered through 0.45 micron injection filter. (Stock solution)
Further pipette 2.5 ml of the above stock solutions into a 25 ml volumetric flask and dilute up to the mark with diluent.
Further pipette 3 ml of the above stock solutions into a 10 ml volumetric flask and dilute up to the mark with diluent. (67.5 ppm Ranitidine)

Procedure
Inject the standard solution, Accuracy -50%, Accuracy -100% and Accuracy -150% solutions.
Calculate the Amount found and Amount added for Ranitidineand calculate the individual recovery and mean recovery values.

Acceptance Criteria
The % Recovery for each level should be between 98.0 to 102.0%

5. ROBUSTNESS
As part of the Robustness, deliberate change in the Flow rate, Mobile Phase composition, Temperature Variation was made to evaluate the impact on the method.

A. The flow rate was varied at 0.8 ml/min to 1.2 ml/min

Standard solution 45 ppm of Ranitidine was prepared and analysed using the varied flow rates along with method flow rate.

On evaluation of the above results, it can be concluded that the variation in flow rate affected the method significantly. Hence it indicates that the method is robust even by change in the flow rate ±10%.

***Results for actual flow (1.0 ml/min)** have been considered from Assay standard.

B. The organic composition in the Mobile phase was varied from 45% to 55%:

Standard solution 45 ppm of Ranitidine was prepared and analysed using the varied Mobile phase composition along with the actual mobile phase composition in the method.

On evaluation of the above results, it can be concluded that the variation in 10%.

Organic composition in the mobile phase affected the method significantly. Hence it indicates that the method is robust even by change in the Mobile phase ±10%

***** Results for actual Mobile phase composition (50:50) Acetonitrile: 0.1% OPA (pH-3) has been considered from Accuracy standard.

RESULTS AND DISCUSSION

SYSTEM SUITABILITY

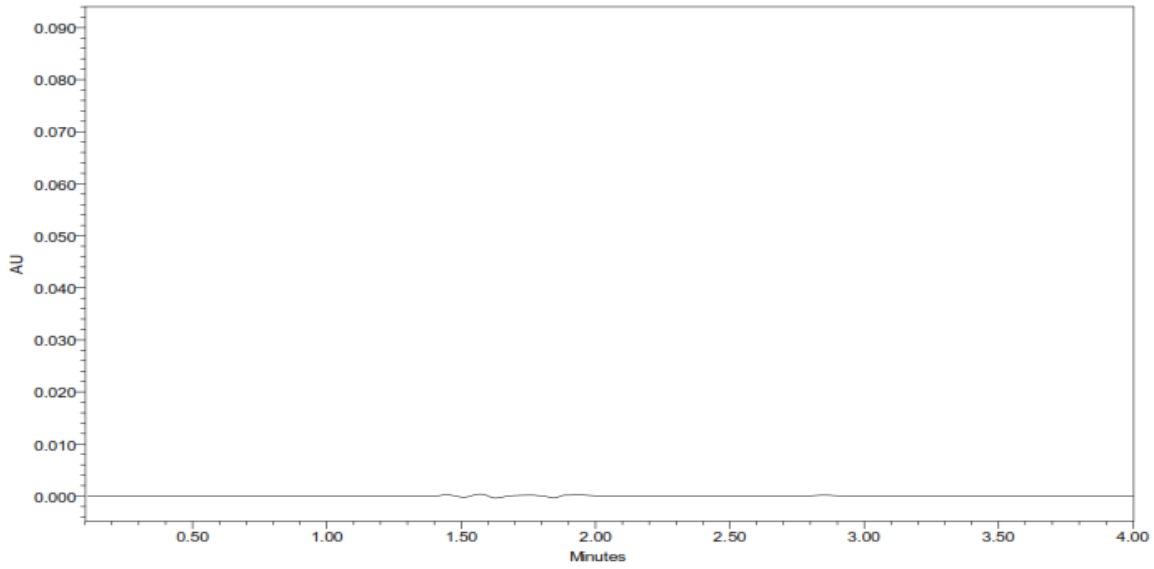

Fig. 2: Chromatogram for Blank

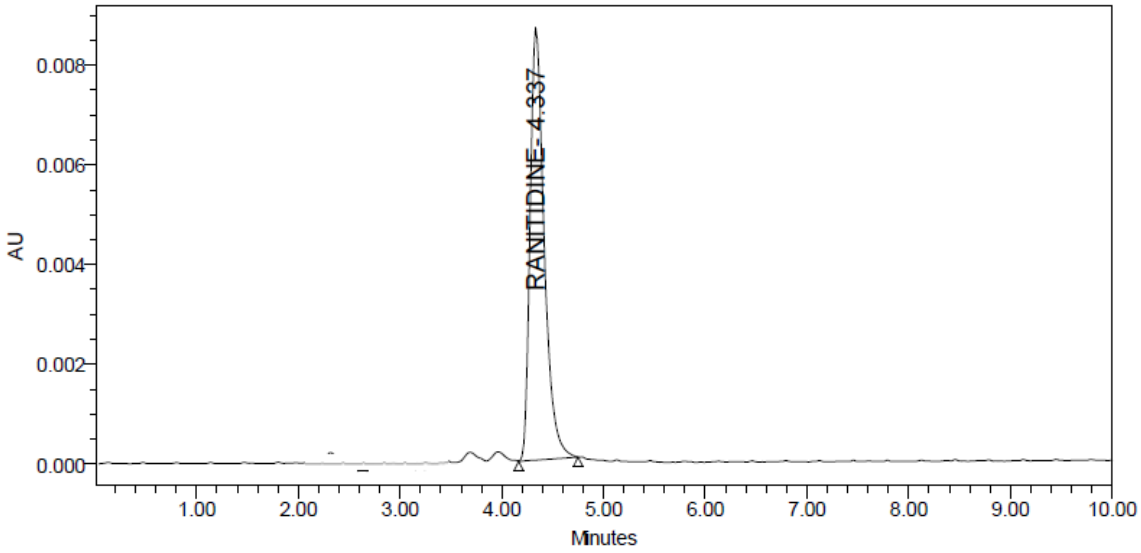

Fig. 3: Chromatogram for system suitability

Table 1: Results of system suitability parameters

S. No.	Name	RT(min)	Area (µV sec)	Height (µV)	USP tailing	USP plate count
1	Ranitidine	4.337	562835	97611	1.33	4842.65

Acceptance criteria

- Theoretical plates must be not less than 2000.
- Tailing factor must be not more than 2.
- It was found from above data that all the system suitability parameters for developed method were within the limit.

ASSAY

Standard and sample solution injected as described under experimental work. The corresponding chromatograms and results are shown below.

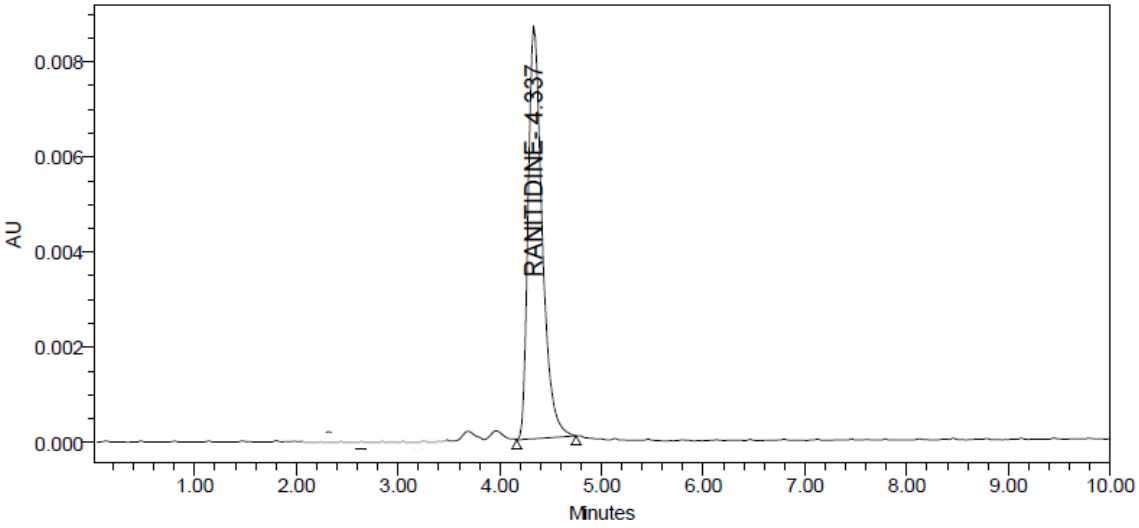

Fig. 4: Chromatogram for Standard

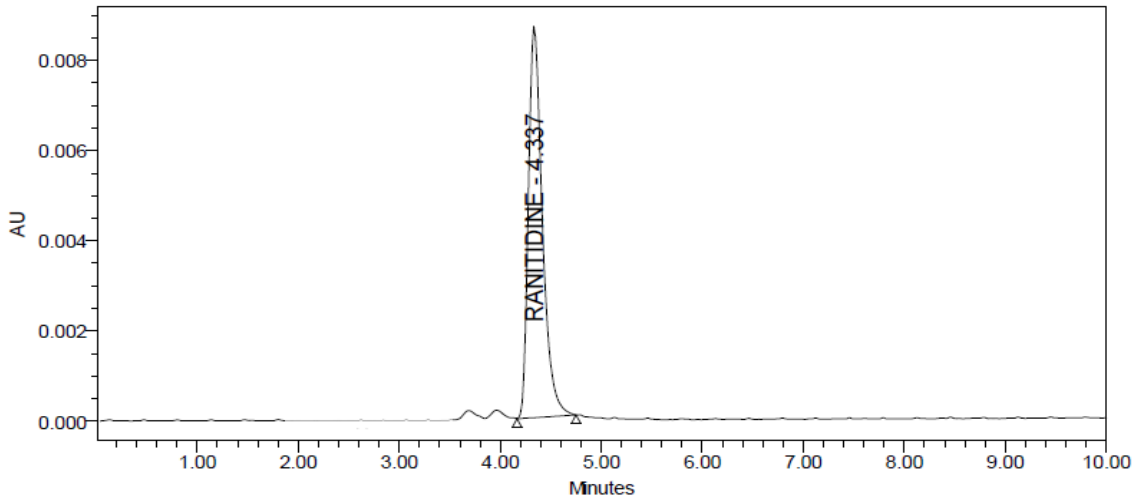

Fig. 5: Chromatogram for Sample

Formula for % Assay

$$\frac{TestArea}{StandardArea} * \frac{StandardConcentration}{SampleConcentration} * \frac{PercentagePurityofDrug}{100} * 100$$

$$\% \, Assay = \frac{566543.3}{565206.3} * \frac{45}{45} * \frac{99.8}{100} * 100 = 100.04$$

Table 2: Results of Assay for Ranitidine

DRUG	Label Claim (mg)	% Assay
Ranitidine	150	100.04

VALIDATION PARAMETERS

1. LINEARITY

The linearity range was found to lie from 15µg/ml to 75µg/ml of Ranitidine and chromatograms are shown below.

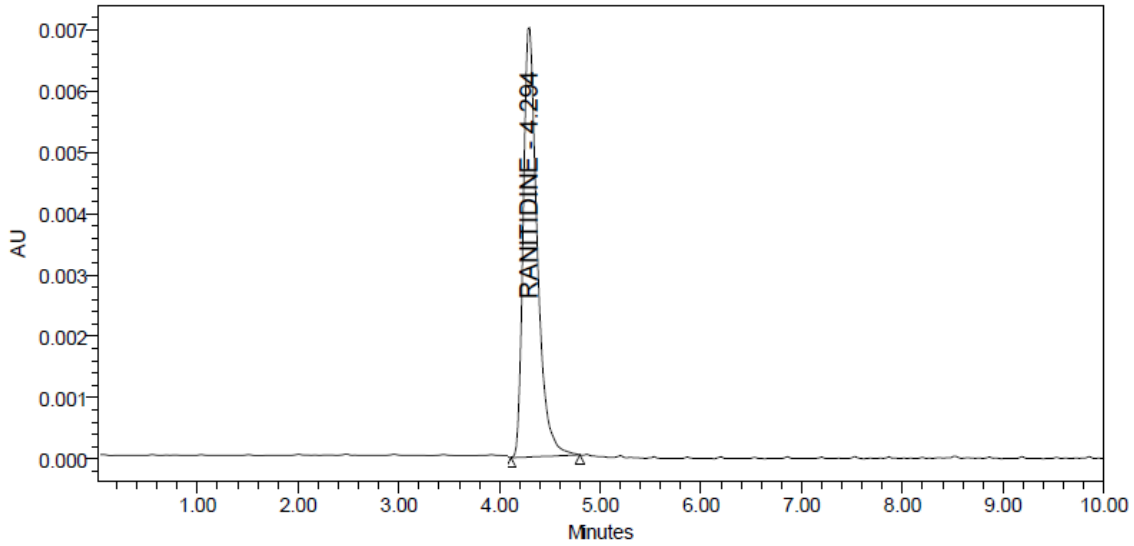

Fig. 6: Chromatogram for linearity-1

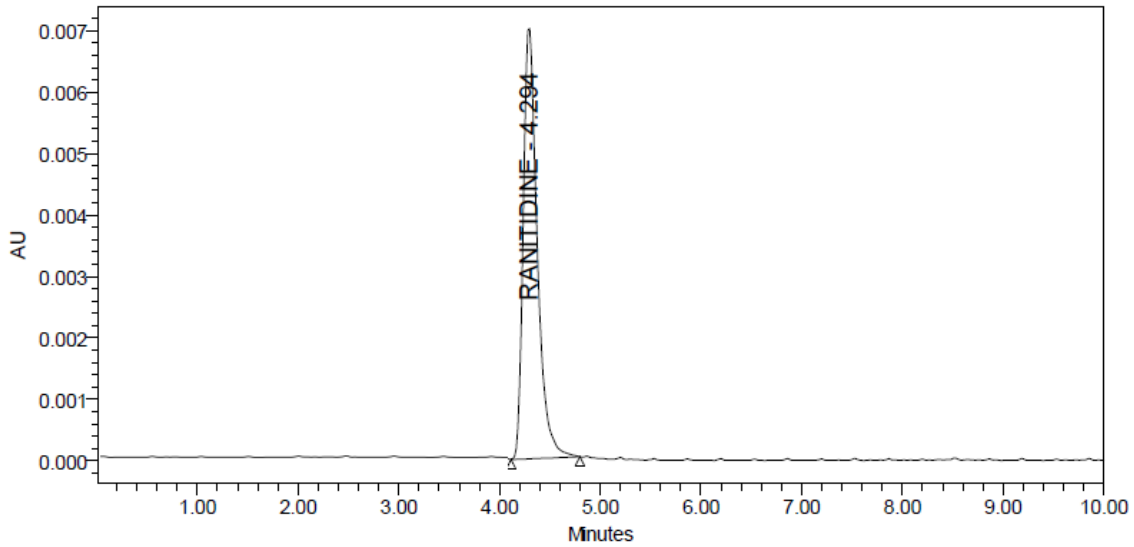

Fig. 7: Chromatogram for linearity-2

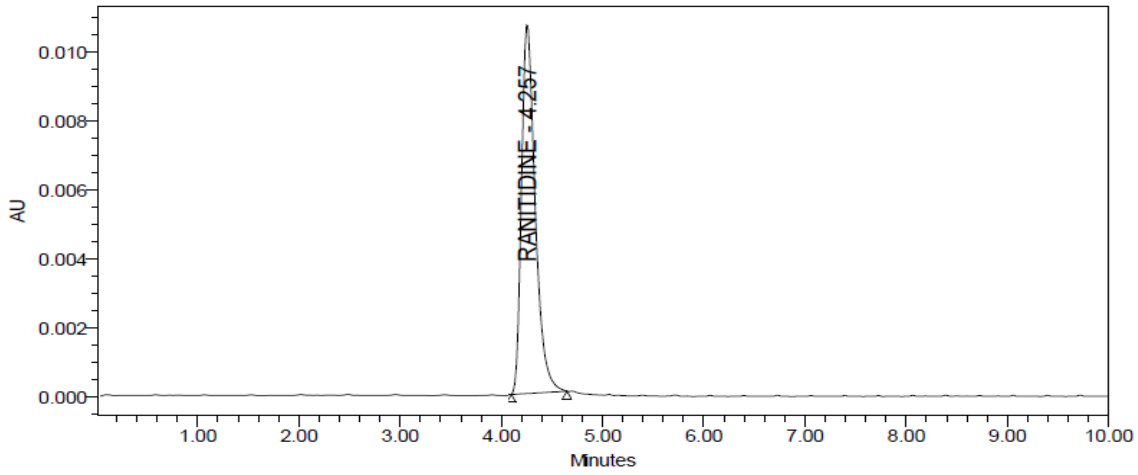

Fig. 8: Chromatogram for linearity-3

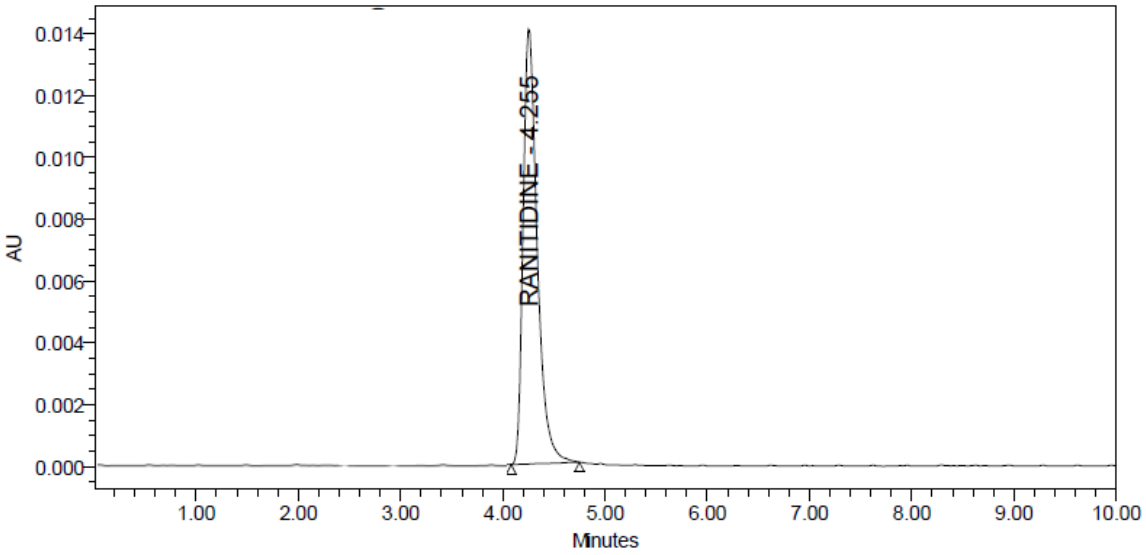

Fig. 9: Chromatogram for linearity-4

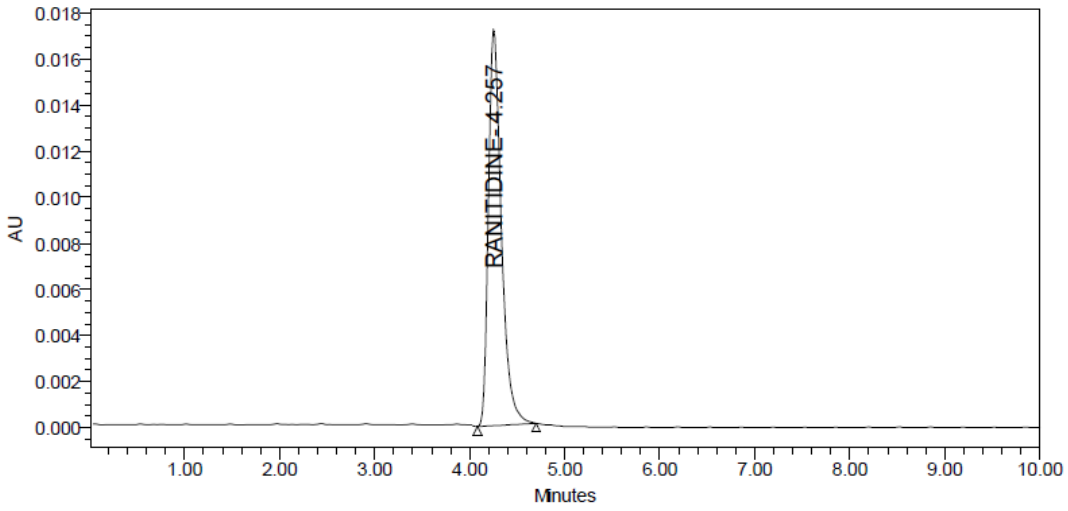

Fig. 10: Chromatogram for linearity-5

Table 3: Area of different Concentration of Ranitidine

S. No	Ranitidine	
	Concentration (µg/ml)	Area
1	**0**	**0**
2	15	196238
3	30	372453
4	45	568974
5	60	756298
6	75	946282

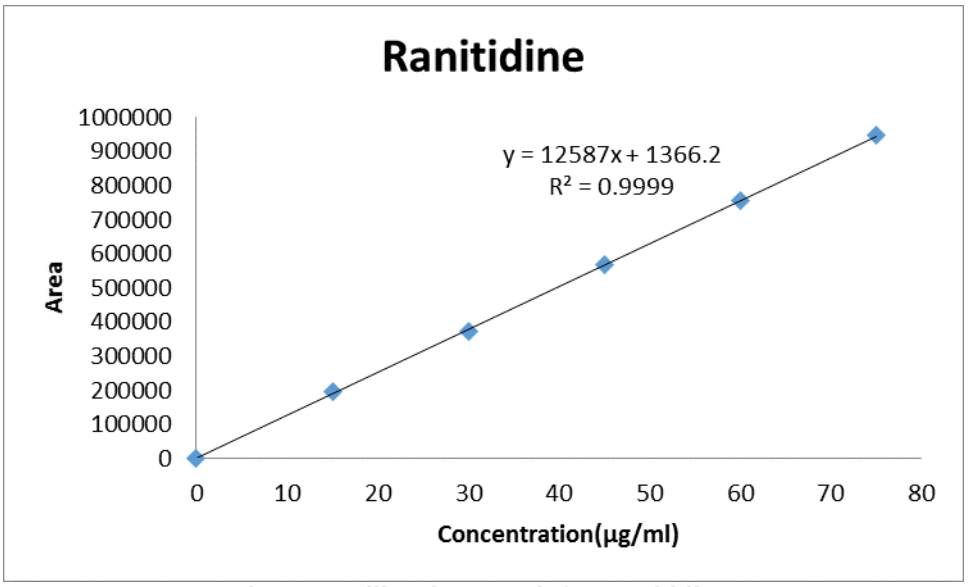

Fig. 11: Calibration graph for Ranitidine

Table 4: Analytical performance parameters of Ranitidine

Parameters	Ranitidine
Slope (m)	12587
Intercept (c)	1366.2
Correlation coefficient (R^2)	0.999

Acceptance criteria

Correlation coefficient (R^2) should not be less than 0.999.

- The correlation coefficient obtained was 0.999 which is in the acceptance limit.

2. PRECISION

Precision of the method was carried out for both sample solutions as described under experimental work. The corresponding chromatograms and results are shown below

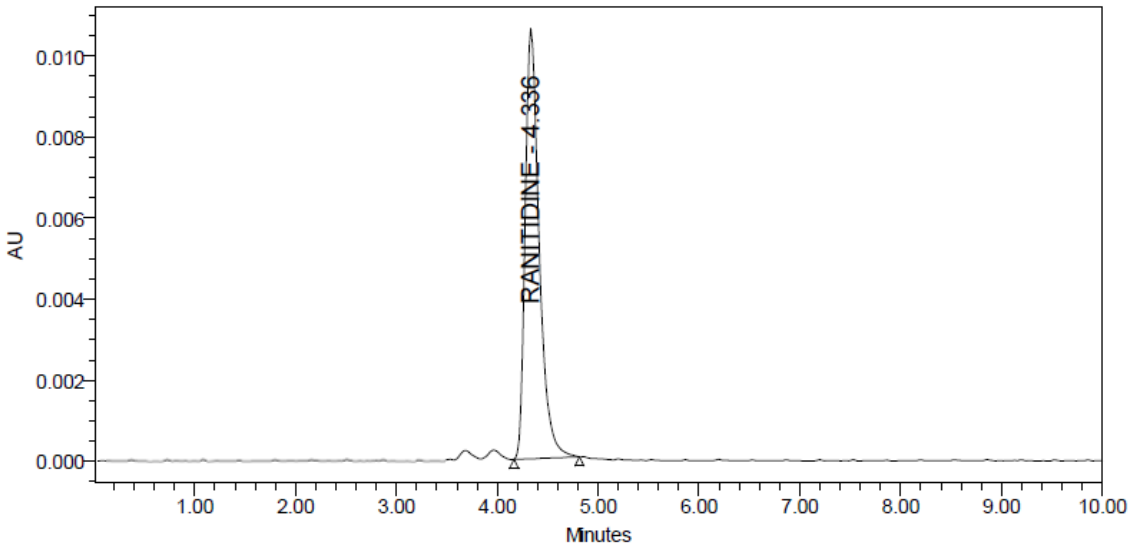

Fig. 12: Chromatogram for Precision-1

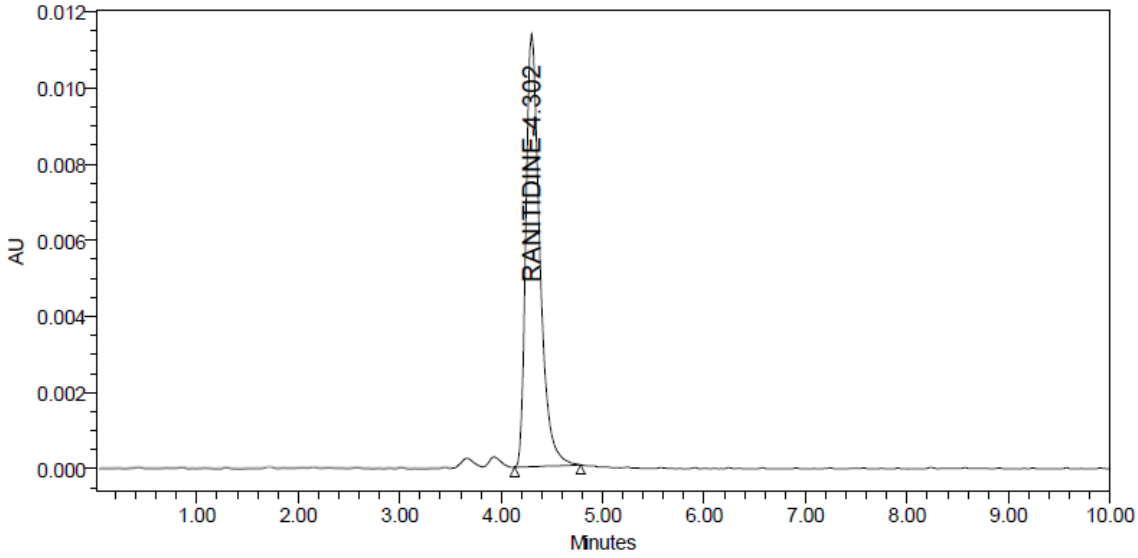

Fig. 13: Chromatogram for Precision-2

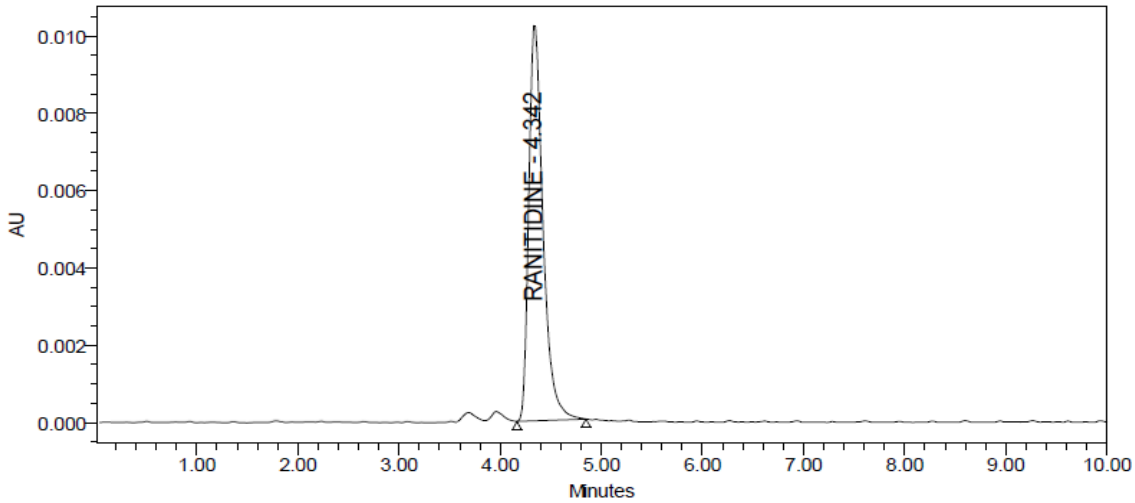

Fig. 14: Chromatogram for Precision-3

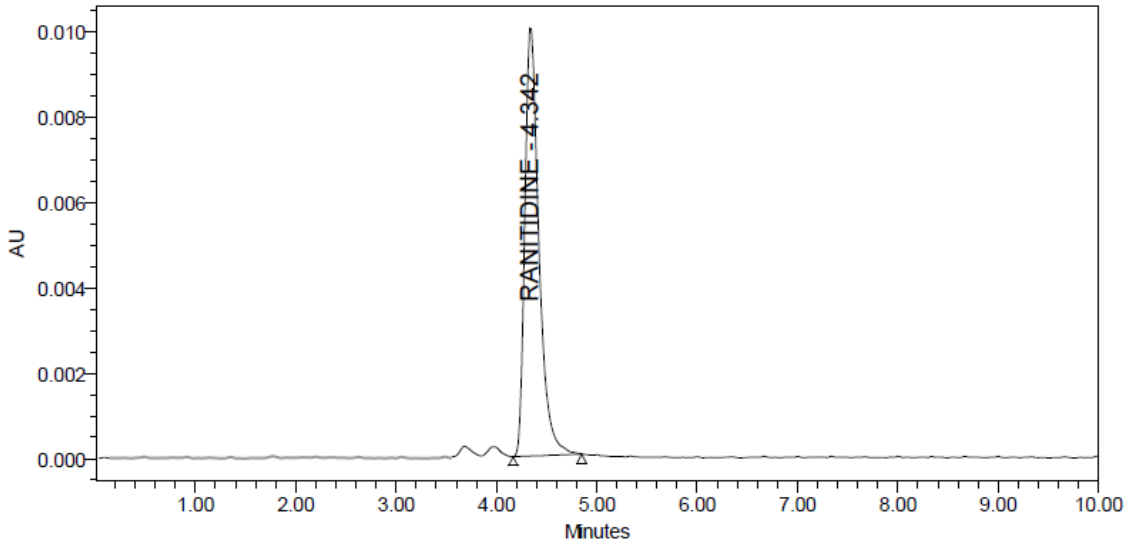

Fig. 15: Chromatogram for Precision-4

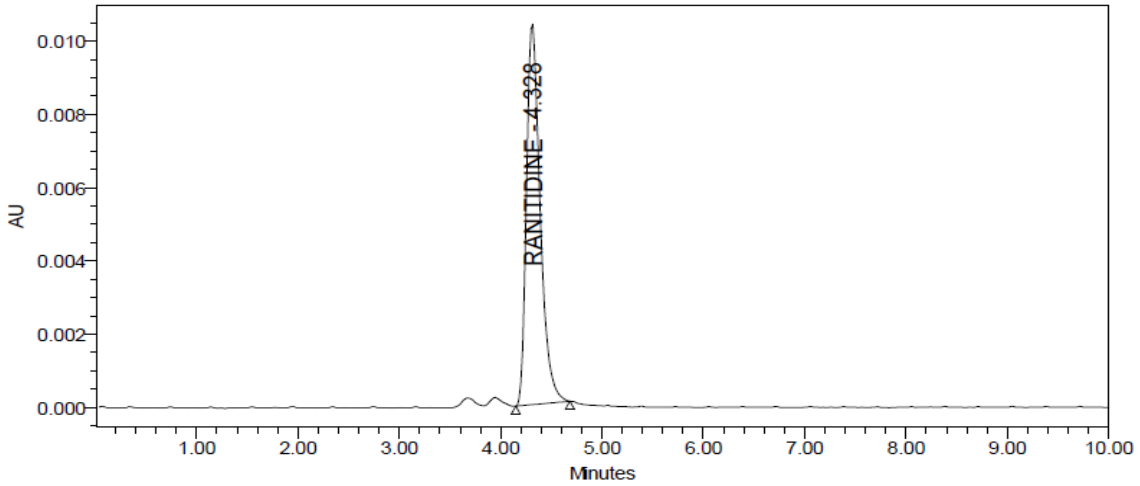

Fig. 16: Chromatogram for Precision-5

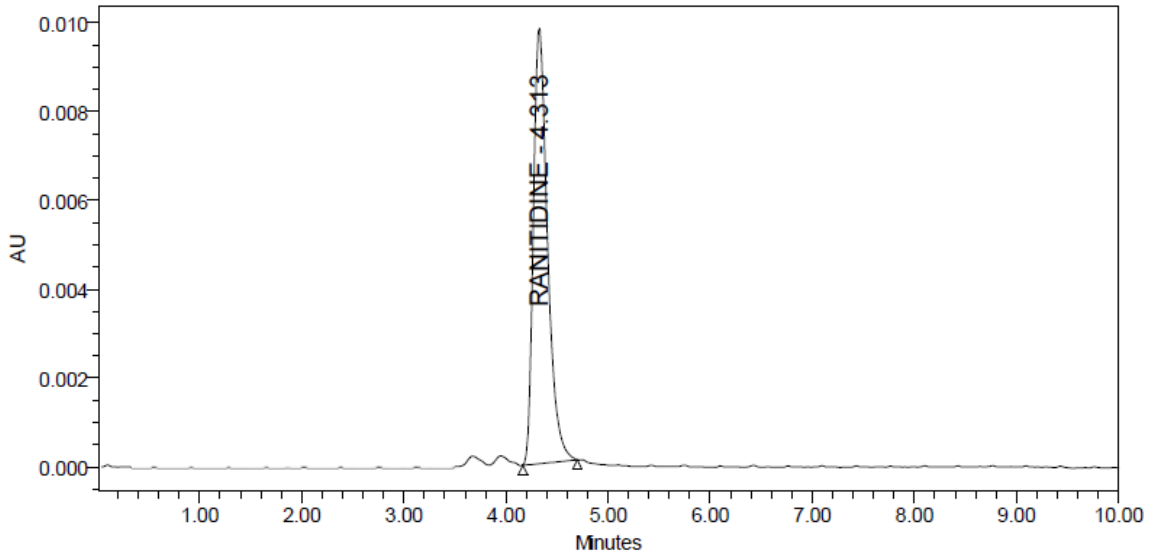

Fig. 17: Chromatogram for Precision-6

Table 5: Results of Precision for Ranitidine

Injection	Area
Injection-1	568845
Injection-2	563387
Injection-3	569745
Injection-4	567745
Injection-5	569453
Injection-6	568465
Average	567940.0
Standard Deviation	2341.4
%RSD	0.4

Acceptance criteria

- %RSD for sample should be NMT 2
- The %RSD for the standard solution is below 1, which is within the limits hence method is precise.

3. INTERMEDIATE PRECISION (ruggedness)

There was no significant change in assay content and system suitability parameters at different conditions of ruggedness like day to day and system to system variation.

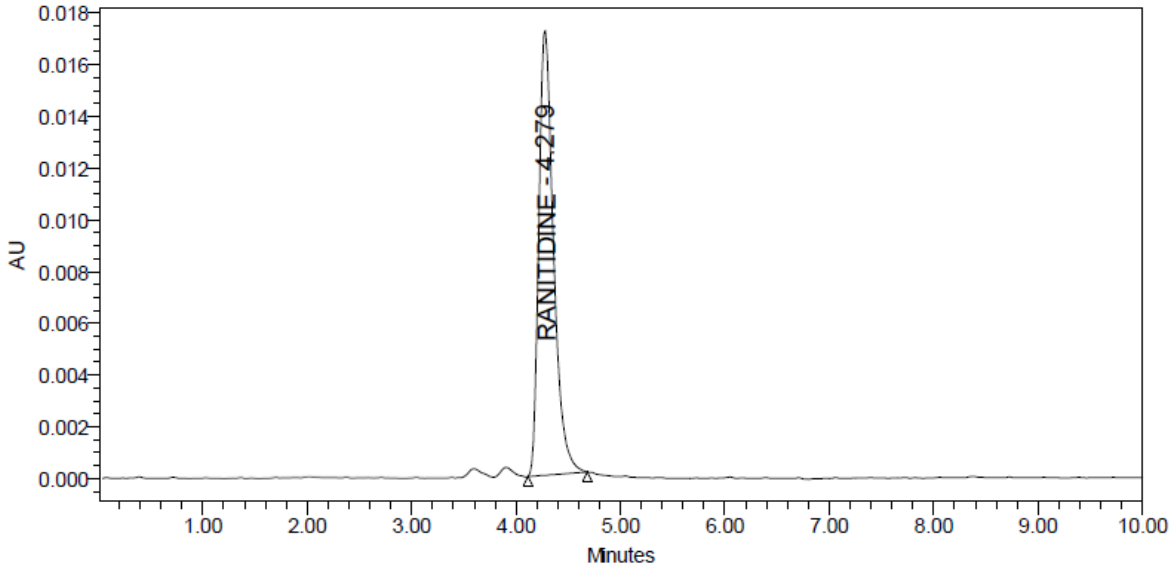

Fig. 18: Chromatogram for ID Precision-1

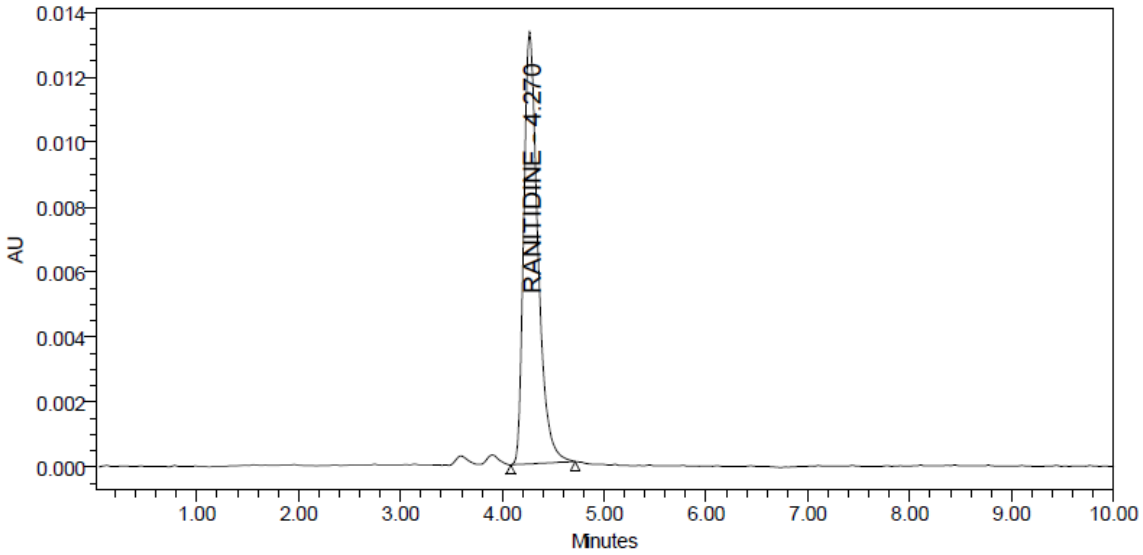

Fig. 19: Chromatogram for ID Precision-2

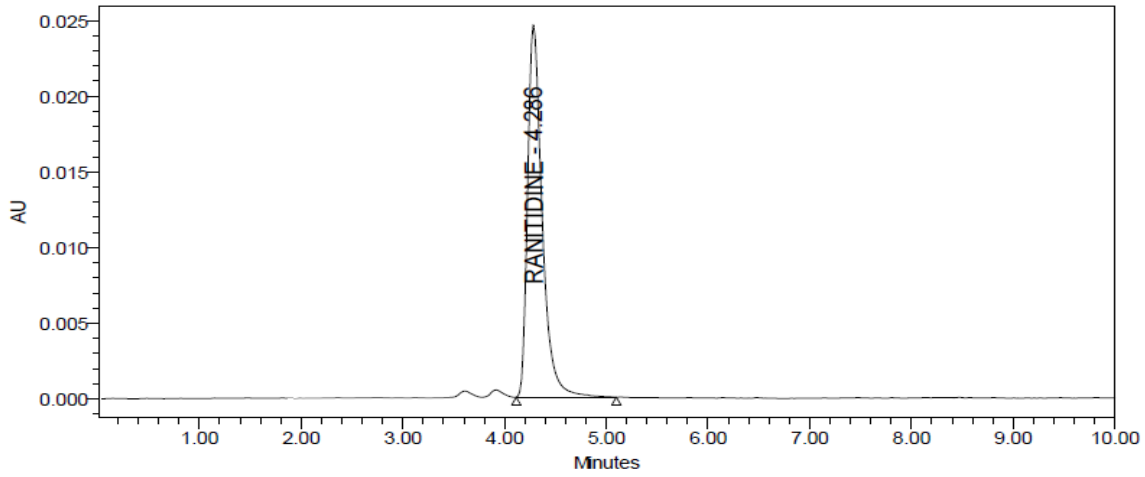

Fig. 20: Chromatogram for ID Precision-3

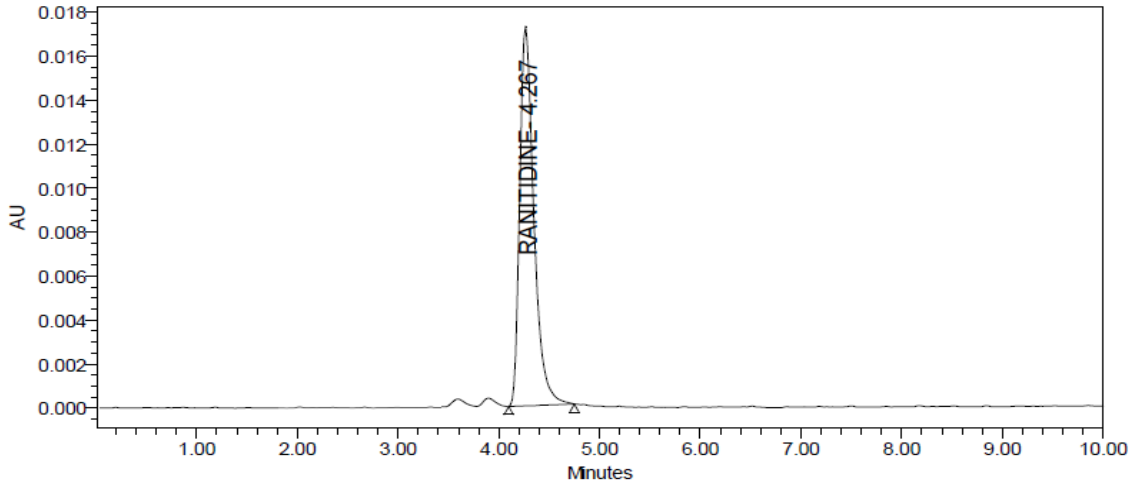

Fig. 21: Chromatogram for ID Precision-4

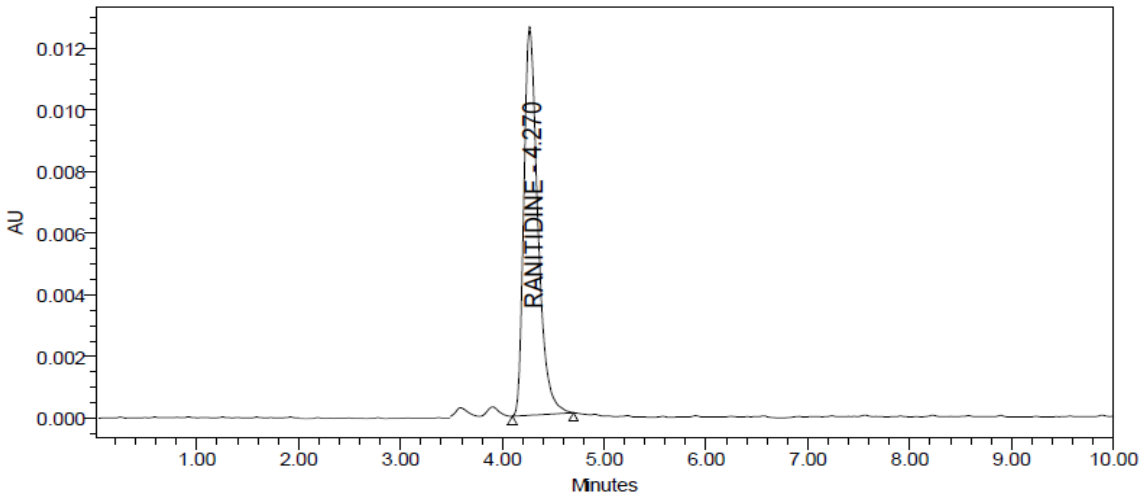

Fig. 22: Chromatogram for ID Precision-5

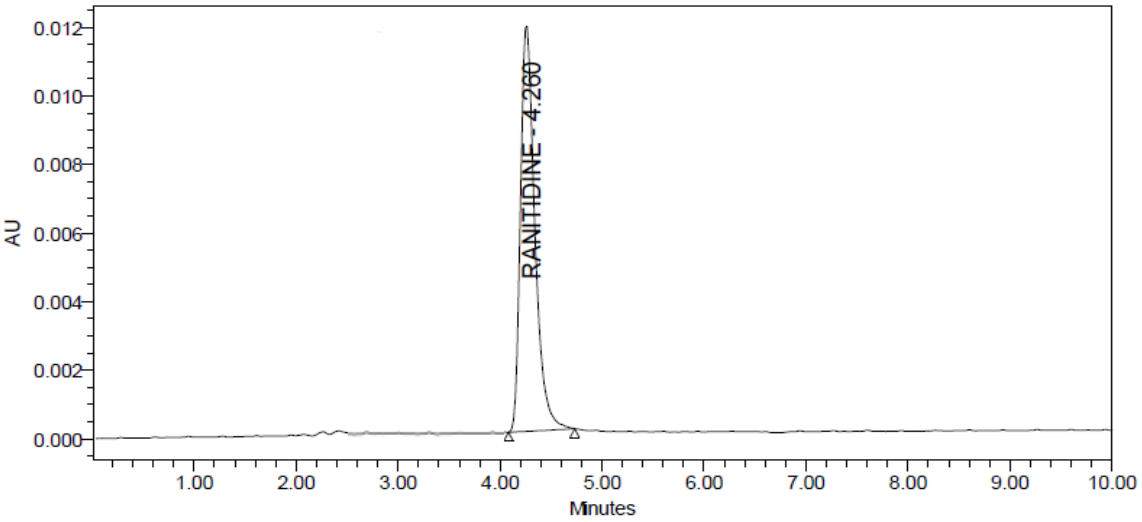

Fig 23: Chromatogram for ID Precision-6

Table 6: Results of Intermediate precision for Ranitidine

Injection	Area
Injection-1	563867
Injection-2	567874
Injection-3	568465
Injection-4	563978
Injection-5	566488
Injection-6	569978
Average	566775.0
Standard Deviation	2477.3
%RSD	0.4

Acceptance criteria

- %RSD of six different sample solutions should not more than 2.
- The %RSD obtained is within the limit, hence the method is rugged.

4. ACCURACY

Sample solutions at different concentrations (50%, 100%, and 150%) were prepared and the % recovery was calculated

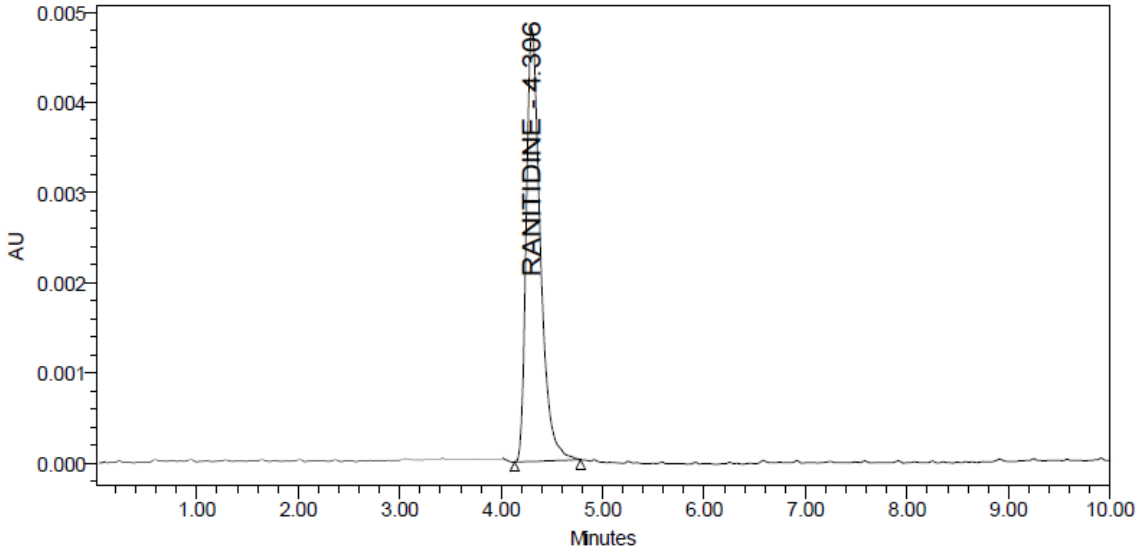

Fig. 24: Chromatogram for Accuracy 50%-1

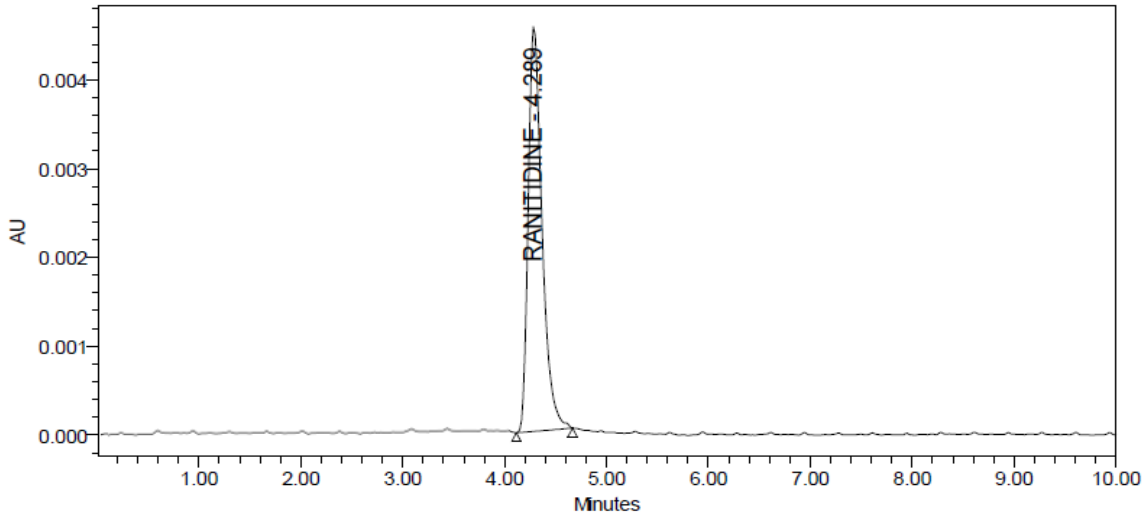

Fig. 25: Chromatogram for Accuracy 50%-2

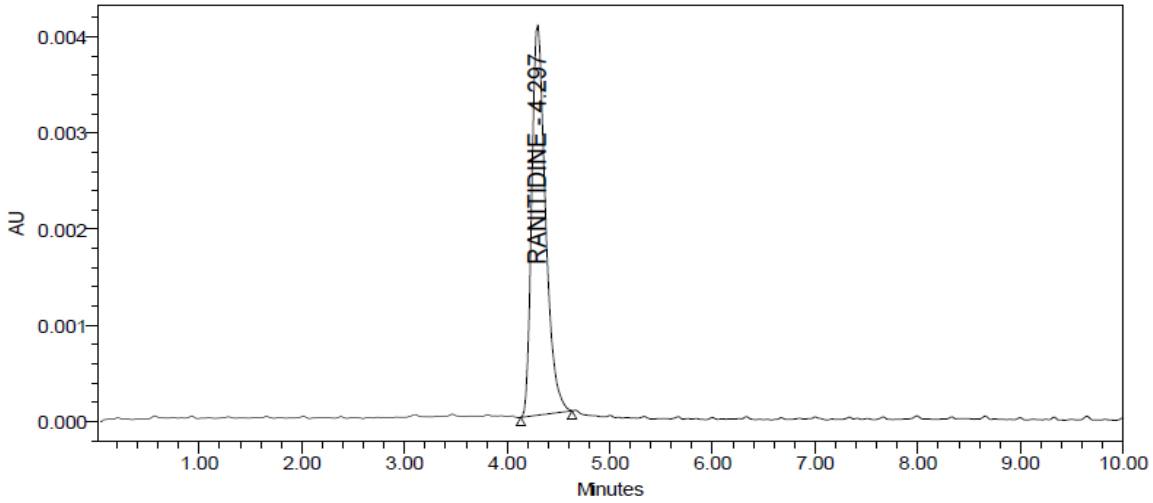

Fig. 26: Chromatogram for Accuracy 50%-3

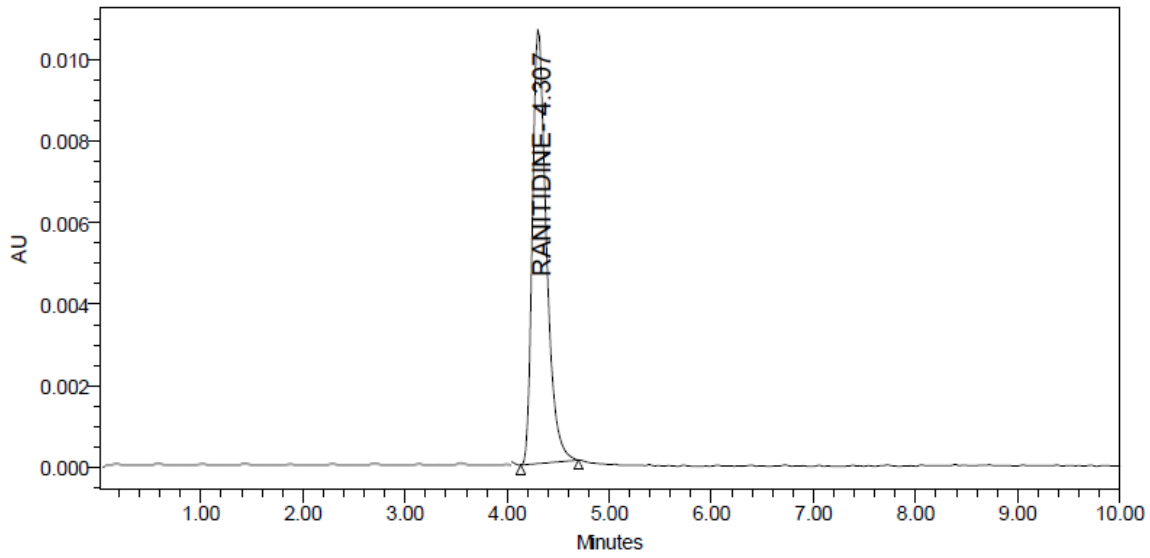

Fig. 27: Chromatogram for Accuracy 100%-1

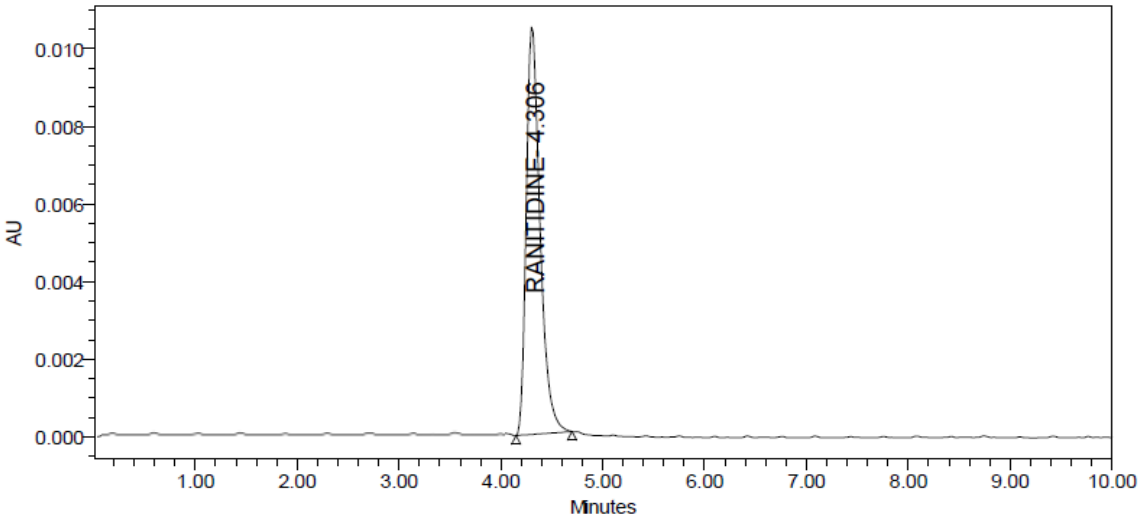

Fig. 28: Chromatogram for Accuracy 100%-2

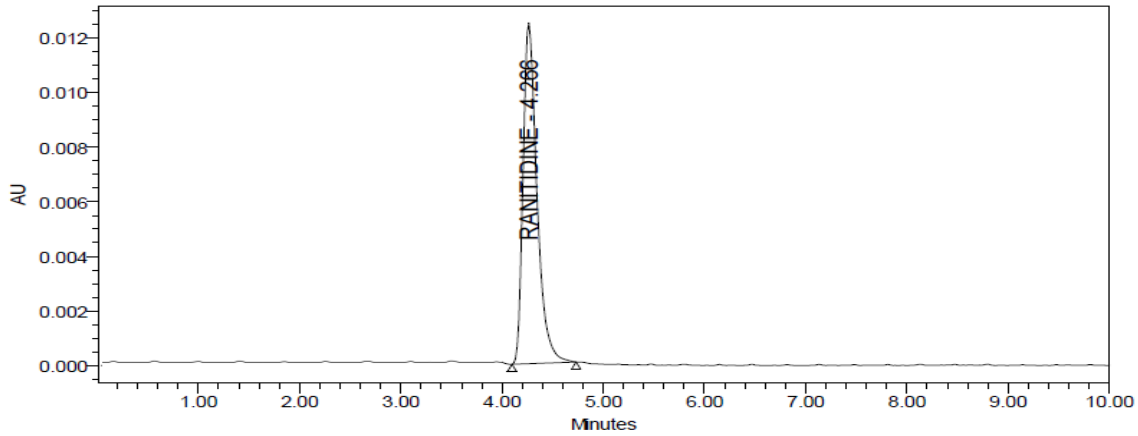

Fig. 29: Chromatogram for Accuracy 100%-3

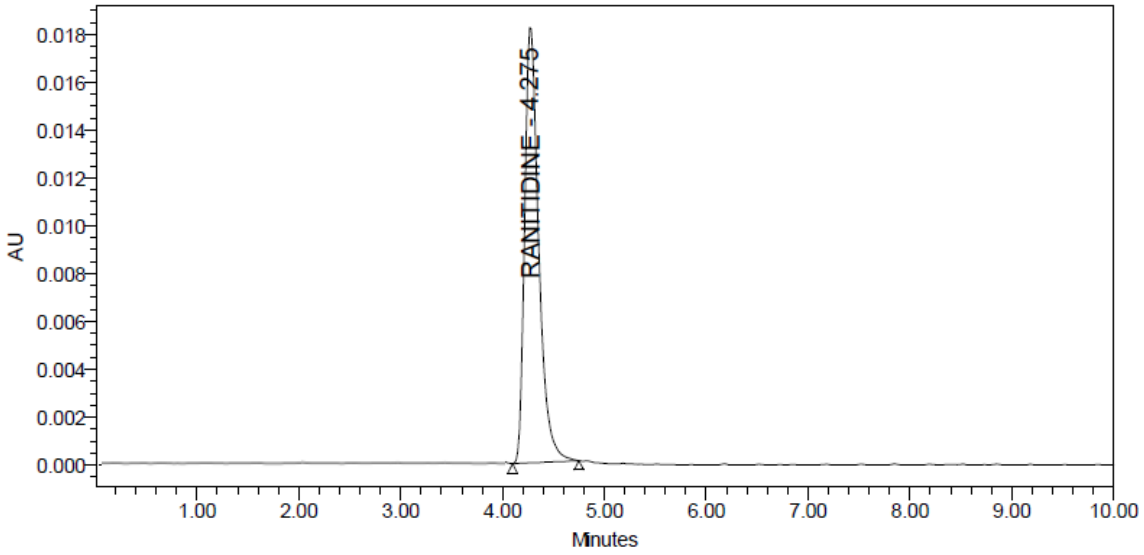

Fig. 30: Chromatogram for Accuracy 150%-1

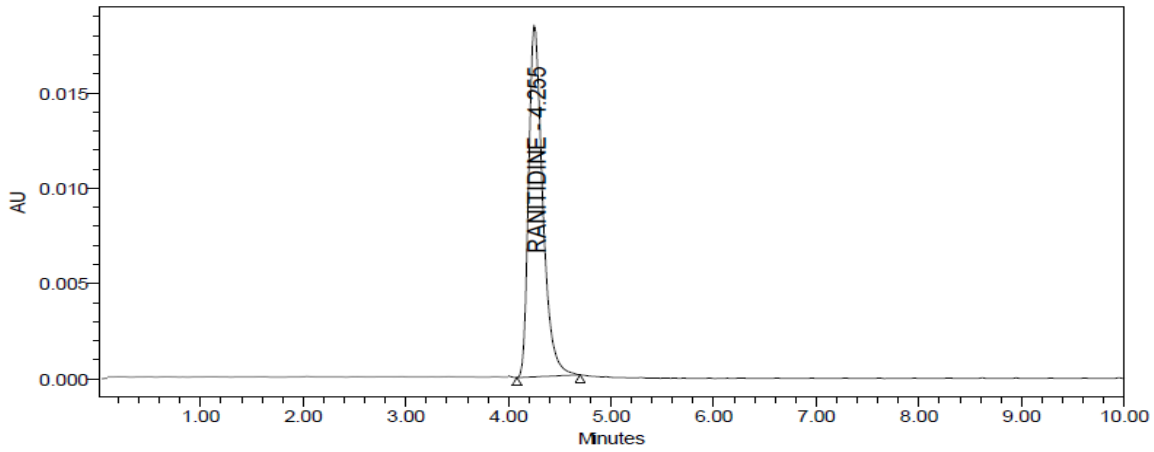

Fig. 31: Chromatogram for Accuracy 150%-2

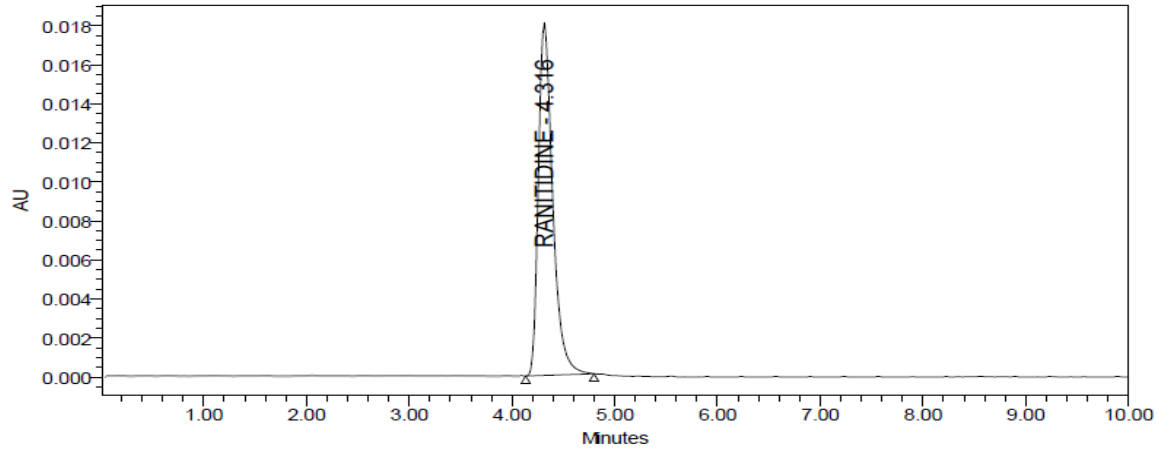

Fig. 32: Chromatogram for Accuracy 150%-3

Table 7: Accuracy (recovery) data for Ranitidine

%Concentration (at specification Level)	Area*	Amount Added (mg)	Amount Found (mg)	% Recovery	Mean Recovery
50%	285615.3	75	75.65	100.86	100.42
100%	567196.3	150	150.23	100.15	
150%	851689.7	225	225.58	100.26	

*Average of three determinations

Acceptance Criteria

- The percentage recovery was found to be within the limit (98-102%).

The results obtained for recovery at 50%, 100%, 150% are within the limits. Hence method is accurate.

5. ROBUSTNESS

The standard and samples of Ranitidine were injected by changing the conditions of chromatography. There was no significant change in the parameters like resolution, tailing factor, asymmetric factor, and plate count.

Variation in flow

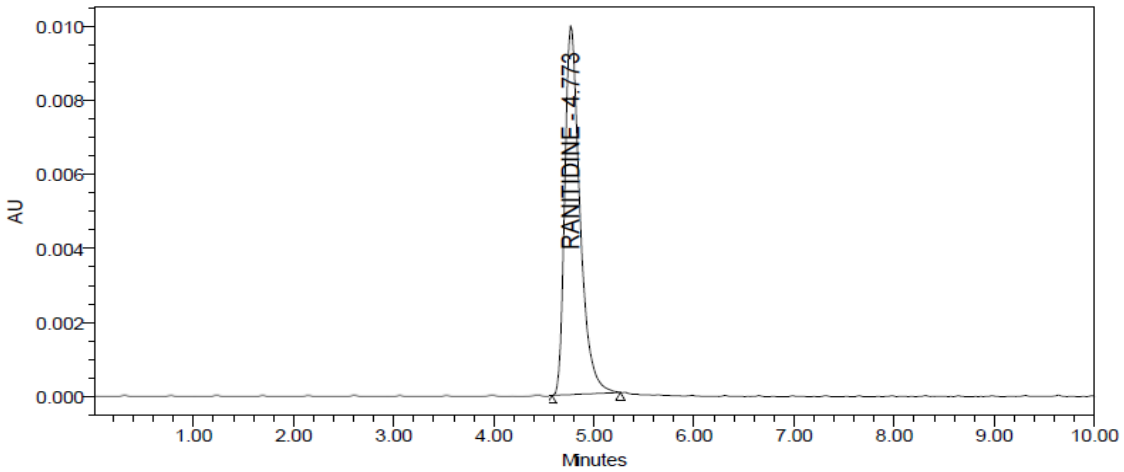

Fig. 33: Chromatogram showing less flow

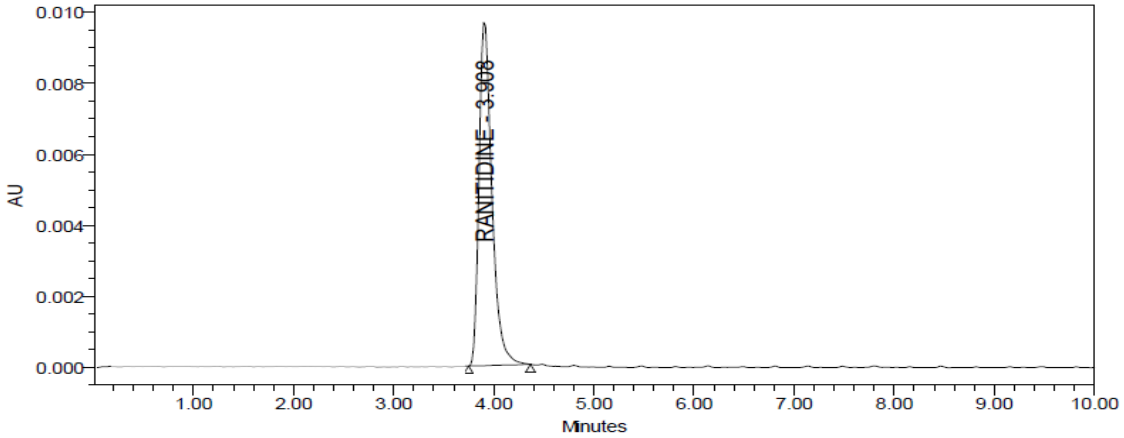

Fig. 34: Chromatogram showing more flow

Variation of mobile phase organic composition

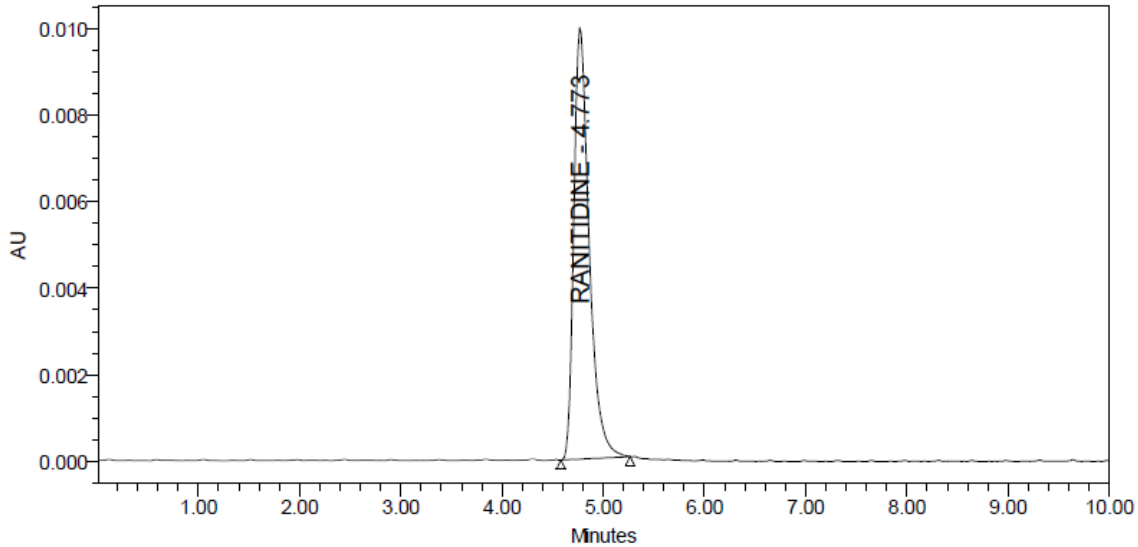

Fig. 35: Chromatogram showing less organic composition

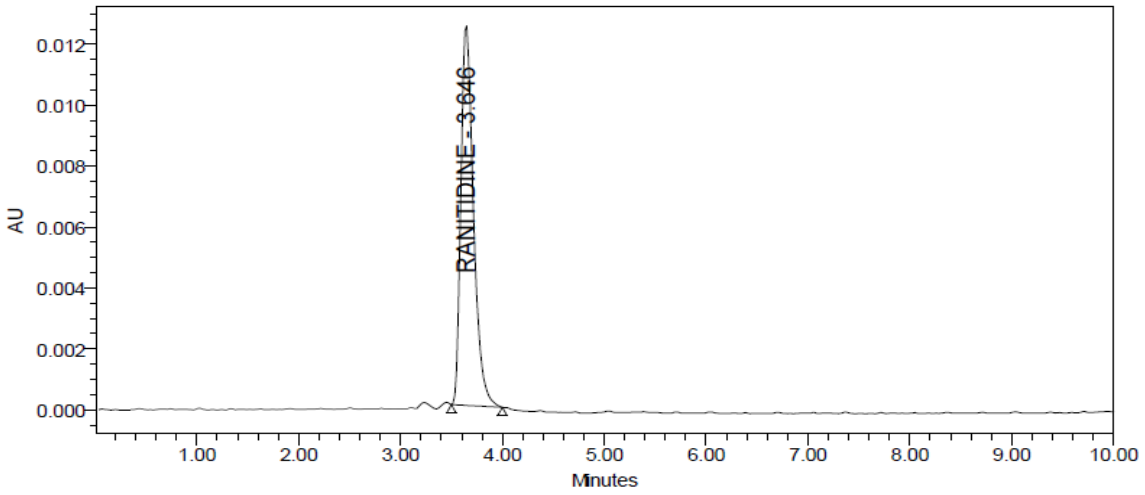

Fig. 36: Chromatogram showing more organic composition

Table 8: Results for variation in flow for Ranitidine

S. No	Flow Rate (ml/min)	System Suitability Results	
		USP Plate Count	SP Tailing
1	0.9	4759.27	1.34
2	1.0	4842.65	1.33
3	1.1	4896.57	1.35

***** Results for actual flow (1.0ml/min) have been considered from Assay standard.

Table 9: Results for variation in mobile phase composition for Ranitidine

S. No	Change in Organic Composition in the Mobile Phase	System Suitability Results	
		USP Plate Count	USP Tailing
1	10% less	4889.33	1.35
2	*Actual	4842.65	1.33
3	10% more	4903.27	1.32

***** Results for actual Mobile phase composition have been considered from Accuracy standard.

Acceptance criteria

The retention time, USP plate count, USP tailing factor obtained for change of flow rate, variation in mobile phase was found to be within the acceptance criteria. Hence the method is robust.

SUMMARY AND CONCLUSION

The estimation of Ranitidine was done by RP-HPLC.

The assay of Ranitidine was performed with tablets and the % assay was found to be 100.04 which show that the method is useful for routine analysis.

The linearity of Ranitidine was found to be linear with a correlation coefficient of 0.999, which shows that the method is capable of producing good sensitivity.

The acceptance criteria of precision is RSD should be not more than 2.0% and the method show precision 0.4 for Ranitidine which shows that the method is precise.

The acceptance criteria of intermediate precision is RSD should be not more than 2.0% and the method show precision 0.4 for Ranitidine which shows that the method is repeatable when performed in different days also.

The accuracy limit is the percentage recovery should be in the range of 98.0% - 102.0%. The total recovery was found to be 100.42% for Ranitidine. The validation of developed method shows that the accuracy is well within the limit, which shows that the method is capable of showing good accuracy and reproducibility.

The robustness limit for mobile phase variation and flow rate variation are well within the limit, which shows that the method is having good system suitability and precision under given set of conditions.

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