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## Quantitative determination of Cimetidine in both bulk and formulations using neutralization titrations

Manish Kumar Thimmaraju, Khaggaswar Bheemanapally, J. Venkateshwar Rao, KRS. Sambasiva Rao and Raghunandan Nerella

**Manish Kumar Thimmaraju**  
**Khaggaswar Bheemanapally**  
**Raghunandan Nerella**  
*Balaji Institute of Pharmaceutical Sciences, Narsampet, Warangal, India, 506331.*

**J.Venkateshwar Rao**  
*Talla Padmavathi College of Pharmacy, Orus, kareemabad, Warangal, Andhra Pradesh, India.*

**KRS.Sambasiva Rao**  
*Head, Department of Biotechnology, Acharya Nagarjuna University Nagarjuna nagar, Guntur, Andhra Pradesh, India*

### ABSTRACT

Cimetidine is the selective H<sub>2</sub> receptor antagonist and inhibits the secretion of hydrochloric acid in the stomach. In the present study, simple titrimetric method was developed. Respective quantities of Cimetidine were taken in aqueous methanol and acetic acid titrated against 0.1N hydrochloric acid and 0.1N perchloric acid using methyl orange and crystal violet as indicators for neutralization and non-aqueous titrations. All the titrations are carried out by running simultaneous blank determinations. The final titer values are subtracted from blank to get actual amount of acid consumed was determined. These methods were found to be sensitive and inexpensive, do not require any sample processing steps and can be utilized for estimation of cimetidine in bulk and formulations.

**Keywords:** Cimetidine, titrimetric analysis, neutralization, non-aqueous titration, H<sub>2</sub> receptor antagonist, assay of cimetidine.

### 1. INTRODUCTION

Cimetidine (2-cyano- 1-methyl- 3-(2-[(5-methyl- 1H-imidazol- 4-yl) methylthio] ethyl) guanidine) is potent histamine H<sub>2</sub> receptor antagonist and inhibits gastric acid secretion (Brimblecombe et al., 1978). A survey of literature had not revealed any titrimetric method for cimetidine; however UV and HPLC analytical methods have been reported (Kelani et al., 2002; Diane et al., 2007). Literature survey revealed that there was no rapid, sensitive and simple titrimetric methods have been reported. It is essential to develop simple and suitable analytical method for its estimation in formulations. Such method should provide better selectivity and sensitivity for routine quality control analysis or similar studies. The present work aims to develop a simple, rapid and sensitive, accurate and economic titrimetric method for the determination of cimetidine in pure form and pharmaceutical preparations using 0.1N Hydrochloric acid and 0.1N Perchloric acid as solvents. These methods do not require any sample processing and extraction steps and can be used for the quality control of these drugs in industry.

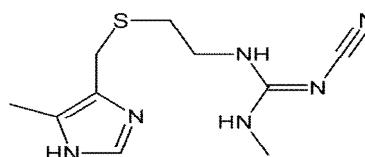


Fig.1. Cimetidine.

**For Correspondence**  
**Manish Kumar Thimmaraju**  
 Associate Professor  
*Balaji Institute of Pharmaceutical Sciences, Narsampet, Warangal, India, 506331.*  
 Email: [manishcancer@gmail.com](mailto:manishcancer@gmail.com)

## 2. MATERIALS AND METHODS

Cimetidine, hydrochloric acid, perchloric acid, glacial acetic acid, methanol, sodium carbonate, methyl orange, potassium hydrogen phthalate, crystal violet, triple distilled water, starch, magnesium stearate, aerosol, talc

### 2.1. Preparation of 0.1N Hydrochloric acid

It was prepared by adding accurately measured 8.5 ml of concentrated hydrochloric acid was diluted to 1000 ml with triple distilled water.

### 2.2. Preparation standard 0.1N Sodium carbonate Solution

It was prepared by dissolving accurately weighed quantity of 5.3 gm of sodium carbonate in distilled water and volume was made up to 1000 ml using standard volumetric flask.

### 2.3. Preparation of 0.1M Perchloric Acid

It was prepared by adding 10.05 gm of perchloric acid to 900 ml of glacial acetic acid and 30 ml of acetic anhydride and final volume was made up to 1000 ml with glacial acetic acid.

### 2.5. Preparation of standard Potassium Hydrogen Phthalate Solution

It was prepared by dissolving 2.5 gm of potassium hydrogen phthalate in glacial acetic acid and volume was made up to 100 ml.

### 2.6. Standardization of 0.1N Hydrochloric acid

Accurately measured quantity of 10 ml of standard sodium carbonate solution was pipetted into a clean conical flask and methyl orange indicator was added. Then the contents in the conical flask were titrated against standard solution of 0.1N hydrochloric acid solution. Titration was carried out until color changes from yellow to pale pink. Results were obtained in triplicate for standardization using the following formula  $N_1V_1=N_2V_2$ , (Where  $N_1$  and  $V_1$  are the normality and volume of standard sodium carbonate,  $N_2$  and  $V_2$  are the unknown normality and consumed volume of hydrochloric acid).

### 2.7. Standardization of 0.1M Perchloric acid

Accurately measured quantity of 25 ml of potassium hydrogen phthalate solution was pipetted into a clean conical flask and crystal violet indicator was added. Then the contents in the conical flask were titrated against standard solution of perchloric acid. Titration was carried out until color changes from violet to emerald green. Results were obtained in triplicate for standardization using the following formula  $M_1V_1=M_2V_2$  (Where  $M_1$  and  $V_1$  are the molarity and volume of the standard potassium hydrogen phthalate;  $M_2$  and  $V_2$  are the unknown molarity and consumed volume of perchloric acid).

### 2.8. Equivalent factors

The exact amount of acid consumed by the drug can be determined by stoichiometric equations were described in Figures 1 & 2. In both of these steps, one mole of drug was undergone

reaction with one of either hydrochloric or perchloric acids. Therefore, Each 1 ml of 0.1N hydrochloric acid or 0.1N perchloric acid is equivalent to 0.025234 gm of cimetidine.

### 2.9. Assay procedure using aqueous titration

Aliquots of cimetidine were prepared by dissolving different amounts of drug (100-500 mg) in 20 ml of 50% methanol. These aliquots were titrated using previously standardized hydrochloric acid after addition of methyl orange as indicator. Color change from yellow to pale pink was observed for end point identification. Results were obtained in triplicates and cimetidine content was assayed.

### 2.10. Assay procedure using non-aqueous titration

Aliquots of cimetidine were prepared by dissolving different amounts of drug (100-500 mg) in 20 ml of glacial acetic acid. These aliquots were titrated using previously standardized perchloric acid after addition of crystal violet as indicator. Color change from violet to emerald green was observed for end point identification. Results were obtained in triplicates and cimetidine content was assayed.

### 2.11. Linearity

To establish the linearity of proposed methods, five separate series of solutions of drug ranging from 100 mg to 500 mg were dissolved in 20 ml of 50% v/v methanol for aqueous and 20 ml of glacial acetic acid, and titrated with 0.1N of Hydrochloric and Perchloric acids.

### 2.12. Specificity

Specificity is the ability of an analytical method to differentiate and quantify the analyte in the presence of other components in the sample (Chandran et al., 2007). The specificity of these methods were determined by adding inert excipients such as starch, microcrystalline cellulose, magnesium stearate and talc individually with known concentration of the drug and titrated by using standard acid solutions.

### 2.13. Estimation from excipient blends

The in-house prepared tablet formulation blends were prepared, since no marketed formulations were available. These tablet blends were prepared by adding immediate release excipients such as starch, microcrystalline cellulose, magnesium stearate and talc. The crushed blend equivalent 200 mg and 400 mg were transferred to conical flask and respective solvents were added; solutions were filtered through Whatman filter paper number (#40) and the filtrate was titrated with standard acid solutions using indicators. Simultaneous blank determinations were conducted to confirm specificity and to nullify the effect of each ingredient. Assay results were shown in Table 3 and 4 and Calibration curves were shown in figure-3 and 4

## 3. RESULTS & DISCUSSIONS

The mean five normality and molarity values are calculated and approximate values obtained, which were equivalent

to normality of 0.1. Methanol was used to dissolve cimetidine and further diluted to 10 ml with triple distilled water, did not produce any precipitate. The proposed reactions were found to be simple neutralization of basic cimetidine molecule using acidic solvents like hydrochloric and perchloric acids (Figure 1 and 2). During the process of titration, the amount of acid consumed was initially run in blank to nullify the effect of consumption of standard solution.

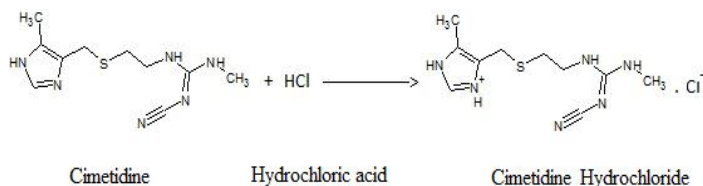


Fig. 2: Aqueous titration.

Table 1 Standardization values of the 0.1N Hydrochloric acid.

Volume of Sodium carbonate added (ml)	Volume of Hydrochloric acid consumed (ml)
10	9.8
10	9.5
10	9.7

Mean volume of Hydrochloric acid consumed = 9.66 ml  
Standard Deviation = 0.15, RSD= 1.58\*  
Normality of Hydrochloric acid consumed = 0.103N

\* Relative standard deviation (n=5)

Table 2. Standardization values of the 0.1M Perchloric acid.

Volume of Potassium Hydrogen phthalate added (ml)	Volume of Perchloric acid consumed (ml)
20	18.6
20	19.2
20	18.8

Mean volume of Perchloric acid consumed = 18.86 ml  
Standard Deviation = 0.30, RSD= 1.61\*  
Molarity of Perchloric acid consumed = 0.106M

\* Relative standard deviation (n=5)

Table – 3 Assay of Cimetidine by Aqueous Titration.

S. no.	Amount of cimetidine added (mg)	Mean volume of Hydrochloric acid consumed (ml)	RSD* (mg)	Mean amount found (mg) †	% Recovery
1	100	3.93±0.06	1.46	99.05	99.05
2	200	8.06±0.17	2.16	203.20	101.60
3	300	11.97±0.20	1.73	301.88	100.63
4	400	15.99±0.25	1.57	403.17	100.79
5	500	20.01±0.19	0.94	504.50	100.90

S. no.	Blend equivalent (mg)	Mean volume of hydrochloric acid consumed (ml)	RSD*(mg)	Mean amount found (mg) †	% Recovery
1	200 mg	8.02±0.13	1.62	202.37	101.19
2	400 mg	16.08±0.25	1.60	405.76	101.29

\*Relative standard deviation (n=5). † Each 1 ml of 0.1N Hydrochloric acid is equivalent to 0.025234 gm of cimetidine.

Table – 4 Assay of Cimetidine by Non-Aqueous titration.

S. No	Amount of cimetidine added (mg)	Mean volume of Perchloric acid consumed (ml)	RSD* (mg)	Mean amount found (mg) †	% Recovery
1	100	4.05±0.11	2.43	102.18	102.18
2	200	7.83±0.20	2.64	197.46	98.73
3	300	12.0±0.15	1.26	302.60	100.87
4	400	16.04±0.25	1.56	404.20	101.05
5	500	19.96±0.26	1.32	503.13	100.63

S. No.	Blend equivalent (mg)	Mean volume of Perchloric acid consumed (ml)	RSD* (mg)	Mean amount found (mg) †	% Recovery
1	200 mg	8.10±0.22	2.76	204.40	102.20
2	400 mg	16.01±0.47	2.90	404.19	101.05

\*Relative standard deviation (n=5). † Each 1 ml of 0.1M Perchloric acid is equivalent to 0.025234 gm of cimetidine.

### Specificity & Linearity

An accurately consumed 11.97±0.20 ml (RSD 1.73) of 0.1N Hydrochloric acid is equivalent to 301.88 mg of cimetidine and 12.0±0.15 ml (RSD 1.26) of 0.1N Perchloric acid is equivalent to 302.60±1.2 mg of cimetidine respectively. Linear regression analysis was performed using Prism 3.0 software and shown in Table 3 and 4. The correlation coefficient was found to be 0.9999 for 0.1N Hydrochloric acid and 0.9998 for 0.1N Perchloric acid.

### 3.2. Assay & Recovery studies

The assay procedure was performed and percent recovery values were determined for actual drug and blend equivalents (Table 3 and 4). The estimated drug content with extremely low value of RSD established the precision of the proposed methods. Recovery experiments using the developed assay procedures further indicated absence of interference from pharmaceutical excipients used in the selected formulation blends.

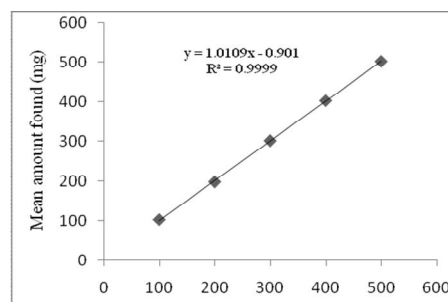


Fig. 3 Calibration curve- Assay of Cimetidine by Aqueous Titration.

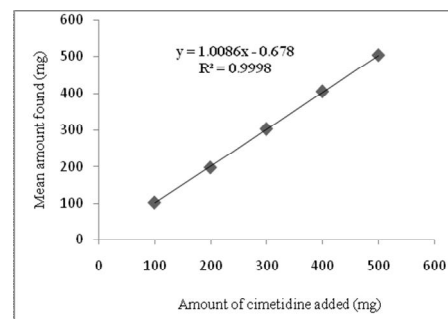


Fig. 4 Calibration curve- Assay of Cimetidine by Non-Aqueous Titration.

#### 4. CONCLUSION

A new titrimetric method has been developed to be routinely applied to estimate cimetidine in bulk and formulations. These methods have been proved to be specific, linear and well recovered. Hence, the method is recommended for routine quality control analysis.

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