e-ISSN: 2249 – 7781
Print ISSN: 2249 – 779X

International Journal of Pharmaceutical Research & Analysis
www.ijpra.com

Research Article

UV METHOD DEVELOPMENT AND VALIDATION OF CIMETIDINE

Yeddala Nandini*, Anna Balaji, B. Sai Prasanna, G. Reshma, M. Pavan, S. Pavan Kumar

Sree Vidyanikethan College of Pharmacy, Sree Sainath Nagar, A.Rangampet, Tirupati-517102, Andhra Pradesh.

ABSTRACT

Ultra violet absorption spectra arise from transition of electrons within a molecule from a lower level to a higher level. A molecule absorb ultraviolet radiation of frequency (U), the electron in that molecule undergo transition from lower to higher energy level. The energy can be calculates by the equation.E1- E0 = hU. Method validation is the process of demonstrating that analytical procedures are suitable for their intended use and that they support the identity, quality, purity and potency of the drug substances and drug products. Simply, method validation is the process of proving that an analytical method is acceptable for its intended purpose.

Keywords: Ultra Violet, Validation, Precision, Method development, Analyte.

INTRODUCTION

Cimetidine is a histamine H2 receptor antagonist that inhibits stomach acid production Cimetidine is mainly used in treatment of heart burns and peptic ulcers Cimetidine was developed in 1971 and came into commercial use in 1977.Cimetidine was approved by UNITED KINGDOM in 1976 and by USFDA in 1979.The development of longer-acting H2 receptor antagonists with fewer drug interactions and adverse effects like Ranitidine and Famotidine, decreased the use of Cimetidine, and though it is still used, Cimetidine is no longer among the more widely used of the H2 receptor antagonists.[1]Ultraviolet and visible (UV-VIS) absorbance spectroscopy is the measurement of attenuation of beam of light after it passes through a sample or after reflection from a sample surface. Absorption measurements can be of a single wavelength or oven an extended spectral range. The region beyond red is called infrared region while beyond violet is called is called as ultra violet.

Corresponding Author

Yeddala Nandini,

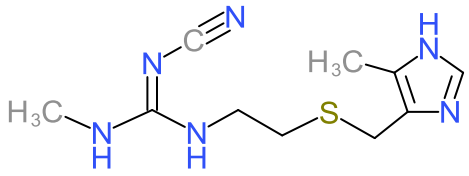
Sree Vidyanikethan College of Pharmacy,
Sree Sainath Nagar, A.Rangampet, Tirupati, AP.

E-mail:nandiniyeddala9@gmail.com

The wavelength range of UV-radiation starts at blue end of visible light (4000Å) and ends at 2000Å.[2].

Drug Profile:
Drug Name: Cimetidine
Molecular Formula: $C_{10}H_{16}N_6S$
Molecular Weight: 252.34 gm/mol
IUPAC Name:1-Cyano-2-méthyl-3-(2-{[(4-methyl-1H-imidazol-5-yl)methyl]sulfanyl}ethyl)guanidine

Chemical Structure:
Figure 1: Structure of Cimetidine



Physical Properties:

State	: Solid
Odour	: Unpleasant odour
Melting point	: 142°c
Solubility	: Freely soluble in alcohol
Dosage form	: Tablets
Storage	: At room temperature

Strength : 200mg and 400mg
pKa : 6.8
Categories : H_2 receptor antagonist

MECHANISM OF ACTION

Cimetidine is a histamine H_2-receptor antagonist. It reduces basal and nocturnal gastric acid secretion and a reduction in gastric volume, acidity, and amount of gastric acid released in response to stimuli including food, caffeine, insulin, betazole, or pentagastrin. It is used to treat gastrointestinal disorders such as gastric or duodenal ulcer, gastroesophageal reflux disease, and pathological hypersecretory conditions.[3] Cimetidine inhibits many of the isoenzymes of the hepatic CYP450 enzyme system. Other actions of Cimetidine include an increase in gastric bacterial flora such as nitrate-reducing organisms.

Route of administration : Oral, Intramuscular, Intravenous
Metabolism : Liver
Bioavailability : 60 – 70%
Protein binding : 13 – 25%
Onset of action : 30 minutes
Elimination half-life : 120 minutes
Duration of action : 4 – 8 hrs
Excretion : Urine

METHODOLOGY

SELECTION OF SOLVENT

Solubility studies of Cimetidine were performed by using suitable solvents like water, ethanol, methanol. The solvent is selected by comparing the good solubility of the drug in different solvents [4]

DISSOLUTION OF DRUG IN SOLVENT

The solvent used for the dissolution of cimetidine after the solubility studies is methanol. The drug has to be dissolved in methanol solvent and it is shaken gently until the drug is dissolved in the solvent. If not, then the beaker containing solvent and drug has to be placed in the ultra sonicator for uniform mixing of drug in solvent methanol [5].

PERFORMING SERIAL DILUTION

After proper dissolution of drug in solvent the serial dilution has to be performed.

SERIAL DILUTIONS

STANDARD: 10mg in 10ml (1000µg/ml)

STOCK-1: 1ml is taken from standard solution and make upto 10ml using methanol (100µg/ml)

STOCK- 2: 1ml is taken from stock-1 and make upto 10 ml using methanol (10µg/ml)

DETERMINATION OF THE Λ_{MAX} VALUE

The determination of the λmax value can be obtained by using UV –Visible spectrophotometer. The stock solution obtained from serial dilution is subjected to UV rays with different wavelengths ranging from 200-400nm. At every wavelength different absorbance values are obtained [6]

UV ANALYTICAL METHOD DEVELOPMENT FOR CIMETIDINE

A solution of Cimetidine at 10µg/ml was prepared by using solvent methanol. Then from this 1ml of solution was scanned in UV region and λmax value was selected as 229nm [7]

METHOD VALIDATION

The procedure of performing numerous assessments designed to verify that analytical test system is suitable for its intended reason and its capable of providing beneficial and legitimate analytical data. Numbers of parameters are:

A) Linearity
B) Accuracy
C) Precision
D) Ruggedness
E) Robustness

Preparation of standard stock solution of Cimetidine

10mg of cimetidine was taken and it is dissolved in 10ml beaker containing 10ml of solvent methanol. Now the concentration of the standard stock solution of Cimetidine is 1000µg/ml [7]

PREPARATION OF WORKING STANDARD SOLUTION

From the above prepared stock solution six working standard solutions were prepared like 0, 5, 10, 15, 20, 25µg/ml respectively and the linearity method was determined [8]

B) ACCURACY

Accuracy of the developed method was carried out by performing recovery study using standard addition method, in which standard drug was added at three different concentration (80%, 100% and subsequently by 120%) to the pre-analyzed formulation (10 µg/ml) [9]

C) PRECISION

The precision of an analytical procedure expresses the closeness agreement between a series of measurements obtained from multiple sampling of the same homogenous sample under the prescribed conditions. Precision of an analytical procedure is usually expressed by the variance, standard deviation or coefficient of variation of a series of measurements [10]

i) INTRADAY PRECISION:

Intraday precision was determined by recording the absorbance of test concentration (10µg/ml) on the same day but at different times in triplicates. Average value was recorded for each time point. % RSD was calculated [11].

ii) INTER DAY PRECISION:

Inter day precision is calculated in a manner similar to intraday precision. The difference lies in only the time, where the absorbance was taken on another day.

D) RUGGEDNESS:

Preparations of 6 working standard dilutions of 10 µg/ml by 2 different analysts were subjected to test absorbance at fixed wavelength in same equipment.

E) ROBUSTNESS

Robustness is ability to remain unaffected by small changes in parameters. It is carried out by measuring the absorbance with the same concentration (10 µg/ml) of solution at different wavelengths (228nm, 229nm, 230nm) [12].

RESULTS AND DISCUSSION

SELECTION OF SOLVENT

Solubility of drug is checked in solvents like methanol, distilled water and ethanol. In water cimetidine is slightly soluble. In methanol Cimetidine is highly soluble.

SELECTION OF ABSORPTION MAXIMA (ΛMAX) FOR ANALYSIS OF CIMETIDINE:

Cimetidine standard solution of concentration 10 µg/ml was scanned in UV-Visible spectrophotometer in range of 200-400nm.Cimetidine shows λmax at 229nm. The proposed analytical method is simple, accurate and reproducible [13]

METHOD VALIDATION

A) LINEARITY

A six point calibration curve was obtained in a concentration range of 5-25 µg/ml.

B) ACCURACY:

Results of recovery study was within the range of 98.5-101.5% indicating that the developed method is an accurate method for the determination of cimetidine.

C) PRECISION: The developed method was found to be as precised as the avg %RSD values for intraday precision and inter day precision study were found to be

D) RUGGEDNESS:

Ruggedness is performed by change in analyst and systems. It was observed that there is no significant changes in assay results which demonstrated that the development method is rugged [14]

E) ROBUSTNESS:

Robustness is ability to remain unaffected by small changes in parameters. It is carried out by measuring the absorbance with the same concentration (10µg/ml) of solution at different wavelength (228, 229, 230 nm) [15]. It was observed that there were no significant changes in assay results which demonstrated that the developed method is robust [16].

F) ASSAY OF CIMETIDINE

The developed UV-method was successfully applied for the estimation of cimetidine. The average percentage purity of cimetidine was found to be 98.56% (w/v) [17].

Table 2: Selection of Wavelength

WAVELENGTH (nm)	ABSORBANCE
200	2.7012
220	2.9219
240	2.1013
260	0.2491
280	0.1912
300	0.1570
320	0.1289

Table 3: Linearity

Concentration (µg/ml)	Absorbance
0	0
5	0.4135

10	0.6588
15	1.0083
20	1.3373
25	1.6696

Table 4: Accuracy

Recovery Level(µg/ml)	Amount Added(µg/ml)	Amount Founded(µg/ml)	%Recovery
05	25	24.59	98.36
20	40	39.23	98.07
30	55	54.47	99.23

Table 5: Intraday Precision

Hours	Concentration (µg/ml)	Absorbance	Average	S.D	%R.S.D
10AM	10	0.8047 0.8128 0.8015	0.8063	0.005824	0.7223
12PM	10	0.8382 0.8426 0.8391	0.8399	0.0023259	0.2769
2PM	10	0.8397 0.8524 0.8459	0.8460	0.006350	0.7506

Table 6: Interday Precision

Days	Concentration (µg/ml)	Absorbance	Average	S.D	%R.S.D
DAY-1	10	0.8047 0.8128 0.8015	0.8063	0.005824	0.7223
DAY-2	10	0.8574 0.8469 0.8488	0.8510	0.00635	0.75
DAY-3	10	0.8631 0.8537 0.8553	0.8573	0.0050	0.583

Ruggedness Data

Table 7: Analyst-1

S.no	Absorbance	Average	S.D	%RSD
1.	0.8278	0.8251	0.002555	0.31
2.	0.8250			
3.	0.8227			

Table 8: Analyst-2

S.no	Absorbance	Average	S.D	%RSD
1.	0.8055	0.8009	0.004757	0.593
2.	0.8012			
3.	0.7960			

Table 9: Robustness Data

Wave length	228nm	229nm	230nm
Trail-1	0.8121	0.8202	0.8003
Trail-2	0.8042	0.8189	0.8281

Trail-3	0.8049	0.8150	0.8168

	229nm	230nm	231nm
X value	0.8070	0.8180	0.8150
S.D value	0.004373	0.002706	0.0139
%RSD Value	0.54	0.33	1.7

Figure 1: Selection of λmax for Cimetidine

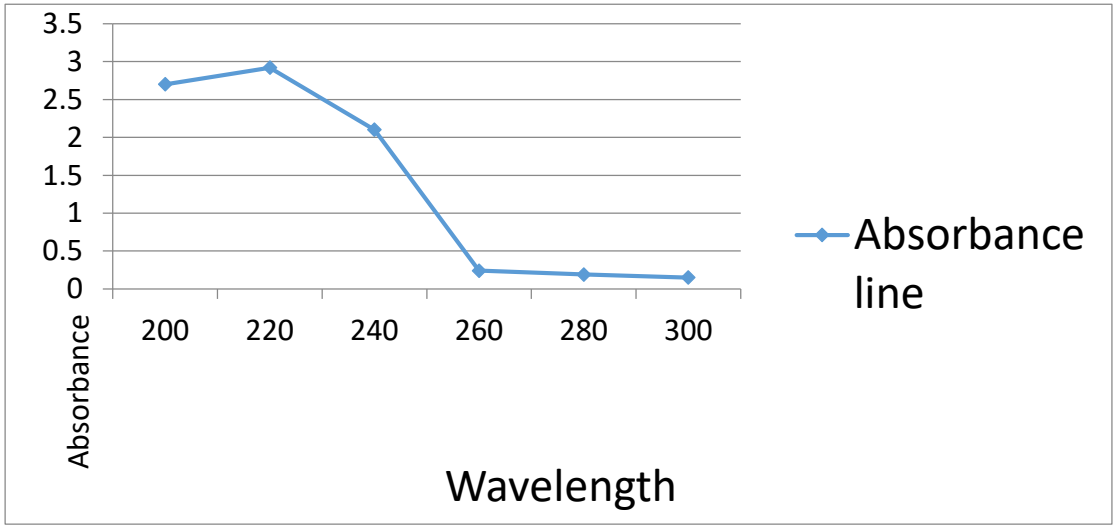
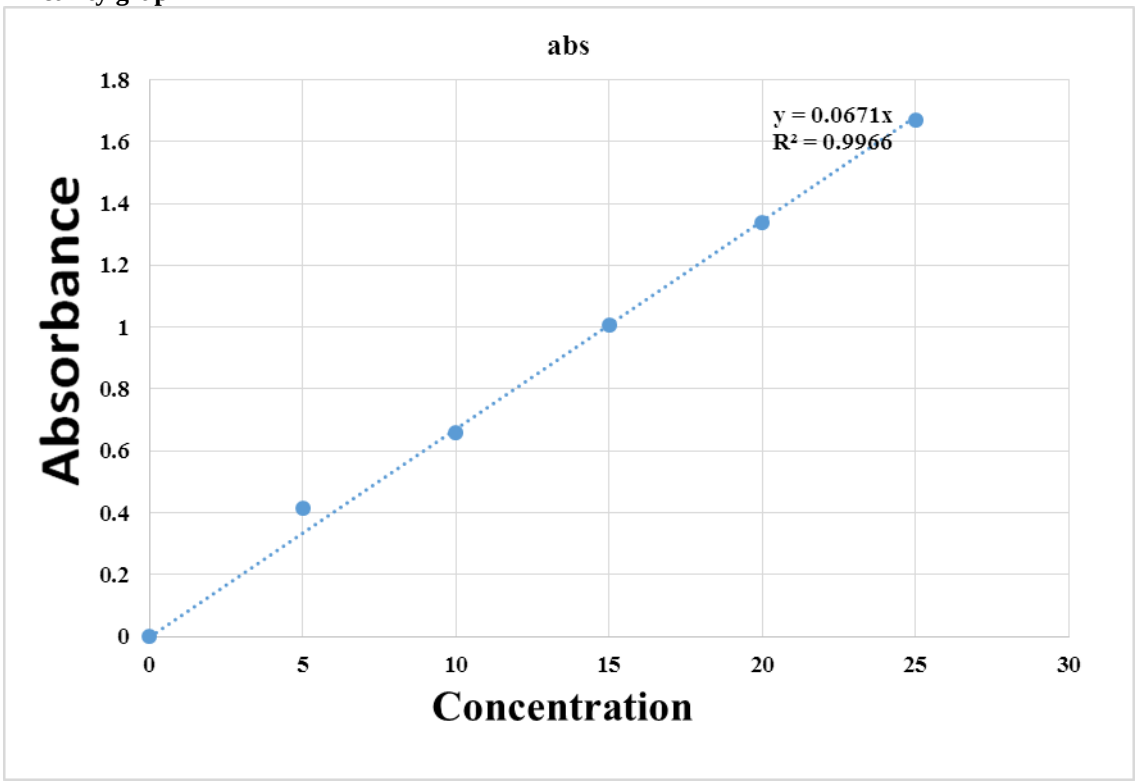


Figure 2: Linearity graph



SUMMARY

Cimetidine is a histamine H_2 receptor antagonist that inhibits stomach acid production. Cimetidine is mainly used in treatment of heart burns and peptic ulcer. A Simple, accurate and precise UV method was developed for estimation of cimetidine. Absorption maxima (λmax) of cimetidine in methanol was found to be 229nm.The assay method using UV spectrophotometer is developed and validated by parameters like accuracy, precision , linearity, ruggedness, robustness. The accuracy of the method was checked by recovery experiment performed at 3 different levels i.e.., 80%, 100%, 120%. The %recovery was found to be in the range of 98-102%.The low values of %RSD are indicative of accuracy, reproducibility of the method. The precision of method was studied as intraday and interday variations. Ruggedness of the proposed method was studied with help of 2 analysts is found be rugged.

CONCLUSION

A simple and effective UV method was developed and validated for the quantitative determination of Cimetidine. This method was considered specific, linear, accurate, precise, and robust for a quick determination of according to the ICH guidelines.

ACKNOWLEDGEMENT

Nil

CONFLICT OF INTEREST

No interest

REFERENCE

1. Wijetunge W and Perera BGK, *et al.* Preparation of Liquid Medicinal Soap Products Using Adhatoda Vasica (Adhatoda) Leaf Extracts. *International Journal of Multidisciplinary Studies*, 2(2), 2015, 73-81.
2. Rakesh KS, Mansi C, Gagandeep K, Arashmeet K, Sandeep A, *et al.* Formulation Development and Anti-microbial Evaluation of Poly Herbal Soap, *Plant Archives*. 19(2), 2019, 1342-1346.
3. Ravi Shankar S. Text book of pharmaceutical analysis. 3rd edition. Tiruelveli. Rx publications, 2006.
4. Sharma B.K.Text book of instrumental of chemical analysis. 27th edition. Geiol publishing house, 2011.
5. Beckett A.H, Stenlake J.B, *et al.* Practical pharmaceutical chemistry, 4th edition-part two. CBS publications, 2017.
6. Sharma Y.R. Elementary organic spectroscopy principles and chemical applications. Multicolour edition. S. Chand publications, 2007.
7. Indian pharmacopoeia. 2nd edition, 2010, 1484.
8. The Merck index. 14th edition, 2006, 851.1.
9. Barber D, Keuter J, Kravig K, *et al.* A logical stepwise approach to laser diffraction particle size distribution analysis methods development and validation. 1998.
10. Li N, Huang H, Qian HZ, *et al.* Improving accuracy of estimating glomerular filtration rate using artificial neural network.
11. Wagner SD & Sherma J, *et al.* Tablet. Analysis of active ingredient cimetidine in acid reduction tablets by high performance thin layer Chromatography with UV absorption densitometry. 2001.
12. Choi YA, Song IS, Choi MK, *et al.* Pharmacokinetic drug-drug interaction and responsible mechanism between memantine and cimetidine. 2018.
13. Barbhaiya RH & Shukla UA, *et al.* Lack of interaction between nefazodone and cimetidine: a steady state pharmacokinetic study in humans. 1995.
14. Shafi N, Siddiqui FA, Naseem H, Sher N, Zubair A, *et al.* An overview of analytical determination of diltiazem, cimetidine, ranitidine and famotidine by UV spectrophotometry and HPLC technique. 2013.
15. Amini H, Javan M, Ahmadiani A, *et al.* Development and validation of a sensitive assay of valproic acid in human plasma by high performance liquid chromatography without prior derivatization. 2006.
16. Arakawa T, Satoh H, Fukuda T, Sakuma H, *et al.* Gastric mucosal resistance and prostanoid levels after cimetidine treatment in rats. 1988.
17. Nugruhani I & Kartini C. Green method for Acetaminophen and ibuprofen simultaneous assay in combination tablet using FTIR. 2018.