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UV-AUC Method Development and Validation for Estimation of 1h, 1'-H-2, 2'-Bibenzimidazole Impurity in Telmisartan Bulk and Formulation

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ABSTRACT

The aim of present work was to develop an accurate, precise, reproducible and economical UV spectrophotometric method for estimation of 1H, 1'-H-2, 2'-Bibenzimidazole Impurity In Telmisartan Bulk and Formulation**.** This method was based on area under curve of UV spectrum between 235 to 254 nm and validated as per ICH guideline Q2 (R1). The method has followed linearity in the range of 5-30µg/ml. The value of correlation coefficient was 0.998. Satisfactory values of Percent relative standard deviation for the intra-day and inter-day precision indicated that method is precise. Results of the recovery studies (97.63% to 98.66 %) showed accuracy of the method. LOD and LOQ were calculated as 0.3221µg/ml and 0.9761 µg/ml, respectively. The developed method can be used for routine estimation of 1H, 1'-H-2, 2'-Bibenzimidazole Impurity In Telmisartan Bulk and Formulation**.**

Keywords: Telmisartan, UV spectrophotometry, Area under curve, Validation, Impurity

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INTRODUCTION

Telmisartan, is a non-peptide molecule, chemically described as 4'-[(1, 4'-dimethyl-2'-propyl [2, 6'-bi-1H-benzimidazol]-1'-yl) methyl]-[1, 1'-biphenyl]-2-carboxylic acid. Its empirical formula is $C_{33}H_{30}N_4O_2$. Its molecular weight is 514.63. It is indicated in the treatment of essential hypertension. The usually effective dose of Telmisartan is 20, 40 and 80 mg once daily. Some patients may benefit at a daily dose of 20 mg. In cases where the target blood pressure is not achieved, Telmisartan dose can be increased to a maximum of 80 mg once daily. Telmisartan is a white to slightly yellowish solid. It is practically insoluble in water and in the pH range of 3 to 9, sparingly soluble in strong acid (except insoluble in hydrochloric acid), and soluble in strong base.[1]

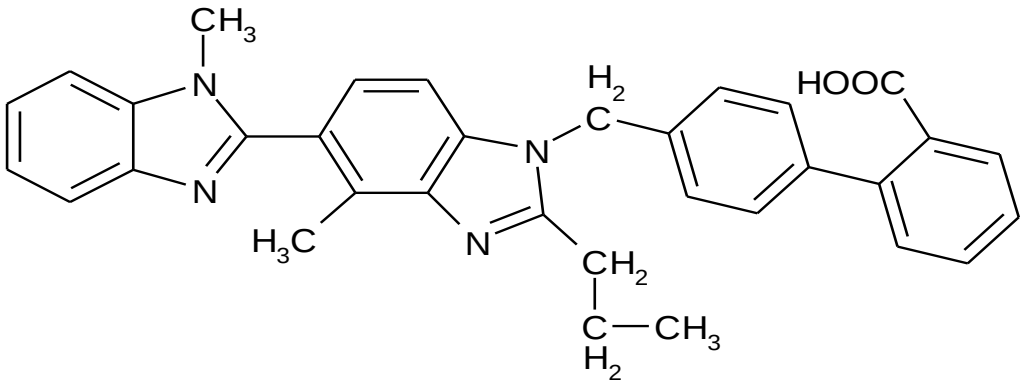
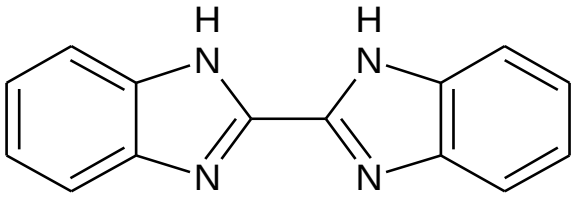


Figure 1: Chemical structure of Telmisartan



1*H*,1'*H*-2,2'-bibenzimidazole

Figure 2: Chemical structure of 1H, 1'-H-2, 2'-Bibenzimidazole Impurity

ICH defines impurity profile of a drug materials is, "A description of the identified and unidentified impurities present in a new drug substance." For Pharmaceutical products, impurities are defined as, "substance in the product that are not the API itself or the excipient used to manufacture it" i.e. impurities are unwanted chemical that remains within the formulation or API in small amounts which can influence Quality, Safety and Efficacy, thereby causing serious health hazards[2,3]. An organic impurity within the manufacturing process along with a good control strategy is an integral part of the quality control of drug substance.

MATERIALS AND METHODS:

Materials:

O-phenylenediamine (AR), Oxalic acid (AR), Methanol (AR), Chloroform (AR), Ethyl acetate(AR) grade was purchased from Merck fine chemicals (Mumbai, India). Telmisartan was obtained as free gift sample from Ranbaxy Laboratories Limited, Gurgaon, India. The pharmaceutical preparation i.e. Telmisartan tablet is procured from local market.

INSTRUMENTS

UV-Visible Spectrophotometer

The maximum wavelength of Telmisartan impurity was found to be 279 nm by using UV-Vis Spectrophotometer (UV-1650 PC) SHIMADZU INC.

Method development:

Preparation of standard solution:

The standard stock solution of Telmisartan was prepared by transferring, accurately weighed, 10 mg of API to 100 ml of volumetric flask. The drug was dissolved with sonication in 50 ml of methanol and volume was made up to the mark by using methanol. The standard stock solution (100 µg/ml) was further diluted with methanol to get the concentration of 10 µg/ml.

Preparation of Impurity solution:

The impurity stock solution of Telmisartan Impurity was prepared by transferring, accurately weighed, 10 mg of Impurity to 100 ml of volumetric flask. The Impurity was dissolved with sonication in 50 ml of methanol and volume was made up to the mark by using methanol. The standard stock solution (100 µg/ml) was further diluted with methanol to get the concentration of 10 µg/ml.

Selection of wavelength range:

The standard solution of both impurity and Telmisartan drug 10µg/ml was scanned between 800 nm to 200 nm in UV spectrophotometer against methanol as blank after baseline correction. Wavelength range was selected around wavelength maxima 296 nm for Telmisartan standard drug and 279 nm for Telmisartan Impurity. Different working standards of Impurity were prepared between 1-100 µg/ml. Various wavelength range were tried and final range between 235-254 nm was selected on the basis of linear relationship between area and corresponding concentration (Figure 3-6)

Area under curve (Area calculation):

This method involves calculation of integrated value of absorbance with respect to wavelength in

indicated range. Area calculation processing item calculates the area bounded by the curve and horizontal axis.

Here horizontal axis represents baseline. Area calculation $(\alpha+\beta) = \int_{\lambda 2}^{\lambda 1} A d\lambda$

Whereas, α is area of portion bounded by curve data and a straight line connecting the start and end point, β is area of portion bounded by a straight line connecting the start and end point on curve data and horizontal axis, λ1 and λ2 are wavelengths representing start and end point of curve region. In this study area was integrated between wavelength ranges from 235 to 254 nm.

Preparation of calibration curve:

Working solutions were prepared from standard stock solution by further dilution with methanol to obtain the concentration of 5, 10, 15, 20, 25 and 30 µg/ml, respectively. These solutions were scanned from 400 to 200 nm and area under curve (AUC) was integrated in the range of 235-254 nm. The calibration curve was plotted between areas under curve against concentration

Method validation

The objective of validation of an analytical procedure is to demonstrate whether the procedure is suitable for its intended purpose. The proposed method was validated for various parameters such as Linearity, Accuracy, Precision, Limit of detection (LOD) and Limit of Quantitation (LOQ) according to ICH Q2 (R1) guideline.

Linearity and Range

The linearity was determined by using working standard solutions between 5-30 µg/ml. The spectrums of these solutions were recorded and area under curve was integrated in wavelength range 235-254 nm. Calibration curve of Area under curve vs. Concentration was plotted after suitable calculation and simple linear regression was performed (Figure 7). Regression equation and correlation coefficient were obtained. The range of solution has been decided according to statistical parameters of generated equation. The results were tabulated in Table 1.

Method Precision study:

Intermediate Precision (Reproducibility)

Intra-day and Inter-day Precision

The intra-day and inter-day precision study of the developed method confirmed adequate sample stability and method reliability. The intra-day and inter-day precision of the proposed method was determined by analyzing the corresponding responses 6 times on the same day and on different day by using 10 µg/ml concentration of impurity. The results were tabulated in Table 2 & 3.

Ruggedness

The method was performed by changing analyst and the method was found to be rugged with mean standard deviation 0.00535 and mean relative standard deviation 1.2256%. The results were tabulated in Table 4.

Robustness

The robustness was performed by change in scanning speed and method was robust with mean standard deviation 0.00355 and mean relative standard deviation 1.1418%. The results were tabulated in Table 5.

Accuracy

The accuracy for the analytical procedure was determined at 80 %, 100 % and 120 % levels of standard solution. Area under curve was measured in the range of 235-254 nm and results were expressed in terms of % recoveries. Three determinations at each level were performed and % RSD was calculated. The results were tabulated in Table 6.

Limit of Detection (LOD) and Limit of Quantitation (LOQ)

Six sets of known concentrations (5-30 µg/ml) were prepared. Calibration curves were plotted for each set. The results were tabulated in Table 7.

RESULTS AND DISCUSSION

An attempt was made to develop a simple and specific AUC spectrophotometric method for the determination of Telmisartan Impurity in Bulk and tablet dosage form. The generated regression equation was (R^2 = 0.998). Where, is area under curve between 235 to 254 nm, C is concentration and R is correlation coefficient. The R^2 value as 0.998 indicate that developed method was linear. The proposed method was found to be precise as % R.S.D values for intraday as well interday precision were satisfactory. The drug at each of the 80 %, 100 % and 120 % levels showed good recoveries (97 % to 98%). Hence, it can be said that this method was accurate. The LOD and LOQ were calculated as 0.3221 µg/ml and 0.9761 µg/ml, respectively. The result of the analysis of pharmaceutical formulation by the developed method was consistent with the label claim, highly reproducible and reliable. The method can be used for the routine analysis of the Telmisartan impurity in tablet dosage form. The validation parameters are summarized in Table 8.

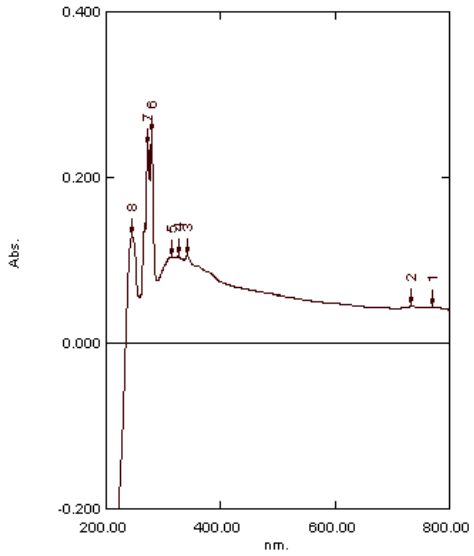


Figure 3: UV spectra of Telmisartan impurity

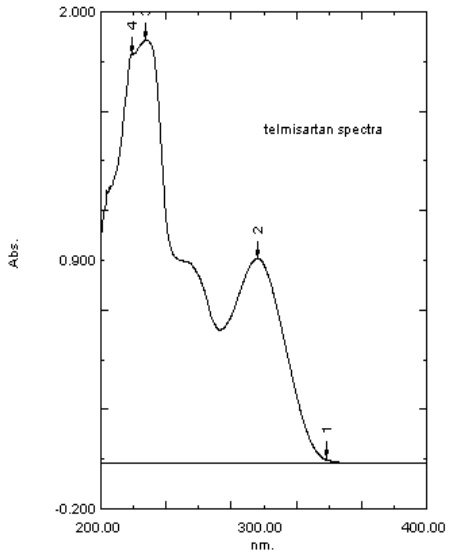


Figure 4: UV spectra of Telmisartan

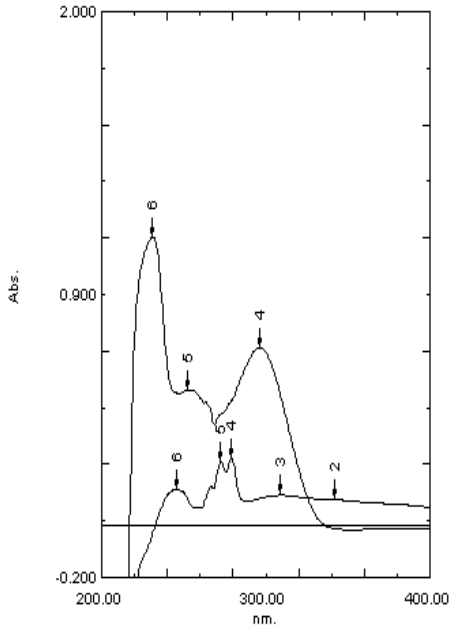


Figure 5: Overlain UV spectra of Telmisartan and impurity

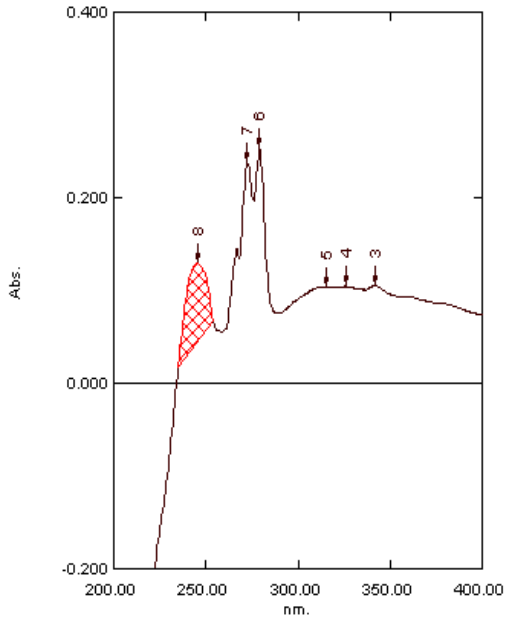


Figure 6: AUC UV spectra of Telmisartan impurity

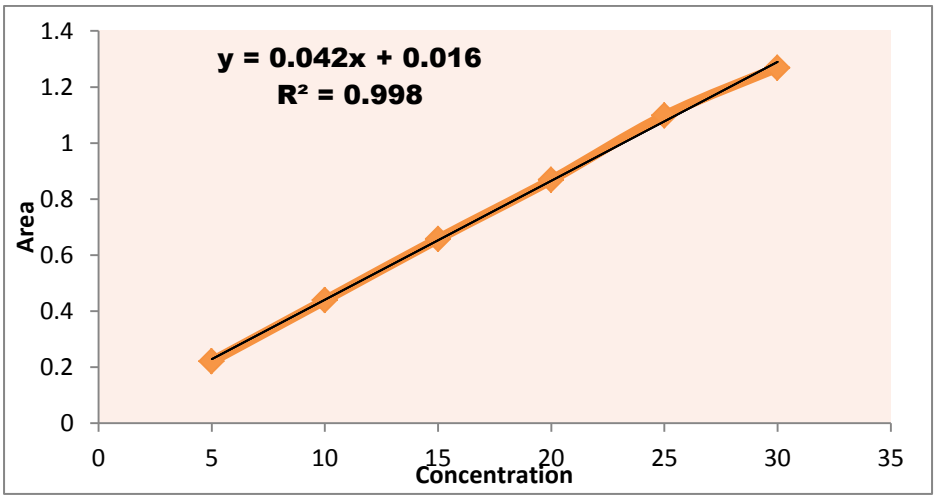


Figure 7: Calibration curve

Table 1: Linearity

Sr. No	Concentration (ppm)	Area
1	5	0.2209
2	10	0.4390
3	15	0.6578
4	20	0.8684
5	25	1.098
6	30	1.269

Table 2: Intra-day Precision

Sr. No	Concentration(ppm)	Area	SD	%RSD
1	10	0.4390		
2	10	0.4431		
3	10	0.4386		
4	10	0.4321	0.0041	0.9384
5	10	0.4356		
6	10	0.4332		

Table 3: Inter-day Precision

Sr. No	Concentration(ppm)	Area	SD	%RSD
1	10	0.4367		
2	10	0.4331		
3	10	0.4486	0.005863	1.3118
4	10	0.4456		
5	10	0.4436		
6	10	0.4387		

Table 4: Ruggedness

Sr. No	Concentration (ppm)	Analyst I	Analyst II	SD I	SD II	%RSD I	%RSD II
1	10	0.4390	0.4478				
2	10	0.4431	0.4368				

3	10	0.4386	0.4426	0.0041	0.0066	0.9384	1.5128
4	10	0.4321	0.4390				
5	10	0.4356	0.4310				
6	10	0.4332	0.4482				

Table 5: Robustness

Sr. No	Concentration (ppm)	Area I	Area II	SD I	SD II	%RSD I	%RSD II
1	10	0.4390	0.4490				
2	10	0.4431	0.4451				
3	10	0.4386	0.4486				
4	10	0.4321	0.4478	0.0041	0.0030	0.9384	0.6726
5	10	0.4356	0.4445				
6	10	0.4332	0.4412				

Table 6: Recovery Study

Sr. No	Drug / Formulation	Percentage recovery			Mean	SD	%RSD
		80%	100%	120%			
1	Bulk	98.00	97.67	97.90	98.033	0.3810	0.3887
2	Tablet	97.93	98.66	98.12	98.13	0.5152	0.5250

Table 7: LOD and LOQ Study :

LOD	**0.3221µg/ml**
LOQ	**0.9761µg/ml**

Table 8: Summary of validation parameters

Parameters	Results
Name of Impurity	1H, 1'-H-2, 2'-BIBENZIMIDAZOLE
λ max	279nm
AUC λ range	235nm-254nm
Beer lamberts Range	5-30µg/ml
Regression coefficient(R^2)	0.998
Slope(m)	0.042
Intercept (c)	0.016
Regression Equation	y = 0.042x + 0.016
Precision(% RSD)	
Intraday	0.9384
Interday	1.3118
Accuracy(%Recovery)	98.033%(Bulk) 98.13%(Tablet)
LOD	0.3221
LOQ	0.9761

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