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DEVELOPMENT AND VALIDATION OF UV SPECTROPHOTOMETRIC METHOD FOR ESTIMATION OF 1H, 1'-H-2, 2'-BIBENZIMIDAZOLE IMPURITY IN TELMISARTAN BULK AND FORMULATION

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ABSTRACT

The process related impurity of Telmisartan i.e: 1H, 1'-H-2,2'-Bibenzimidazole was synthesized**,** characterized and quantified in bulk and formulation. The synthesis of intermediate was carried out by using O-phenylenediamine, oxalic acid. The percentage yield was found to be 78 %. Purification of impurity was done by rescrystallization. The preliminary evaluation was done on laboratory scale via melting point, elemental analysis and TLC. The melting point of impurity was found to be 310-315 ^{0}C. The TLC of impurity was carried by using Chloroform: Methanol: Ethyl Acetate (3:2:1) mobile phase and the R_f was found to be 0.65.The process impurity was synthesized, purified, and characterized by IR, ^{1}H-NMR and UV method was developed for quantification of synthesized impurity. The method was validated as per ICH Q2B guidelines. The UV method was found to be linear, precise, accurate, robust and rugged. Finally 1H, 1'-H-2,2'-Bibenzimidazole impurity was quantified from Telmisartan bulk and its marketed tablet formulation.

KEYWORDS: Validation, Telmisartan, Impurity, 1H, 1'-H-2,2'-Bibenzimidazole.

1. 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]

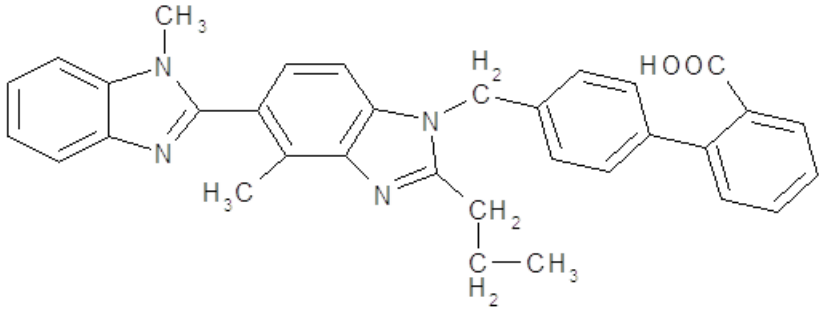
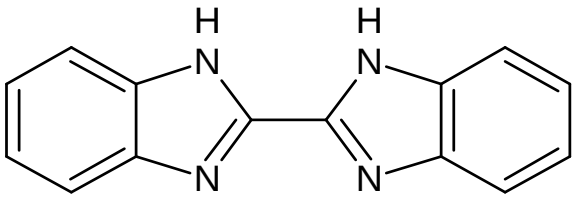


Figure 1: Chemical structure of Telmisartan



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.

2. MATERIALS AND METHODS

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.

3. INSTRUMENTS

3.1 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.

3.2 FT-IR

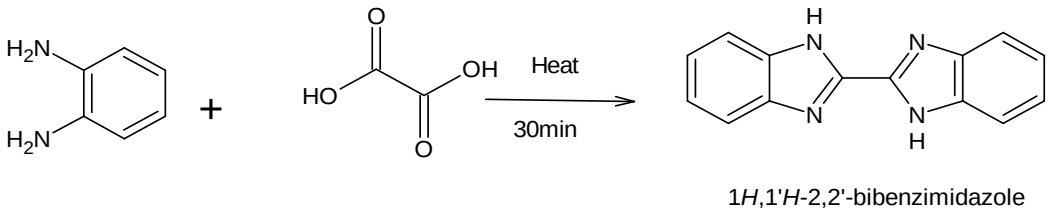
The IR spectra were recorded by using Fourier Transform Infrared Spectrophotometer Model No. 8400S SHIMADZU by KBr press pellet technique.

3.3 NMR

Characterization of impurities was achieved by using Varian NMR Mercury 300 MHz spectrometer, using DMSO as a solvent and TMS as an internal reference standard for the proton experiment. All experiments were conducted at 25°C, and no shift relaxation agents were employed. The ^{1}H and ^{13}C NMR chemical shift values were reported on the δ scale in ppm.

4. SYNTHESIS OF 1H, 1'-H-2,2'-BIBENZIMIDAZOLE IMPURITY

Synthesis of 1H, 1'-H-2, 2'-Bibenzimidazole under sand bath heating(Solvent Free Synthesis)*:* A mixture of O-phenylenediamine(2.2 mmol) and Oxalic acid (1 mmol) in a flask was heated for 30 minutes on a sand bath. The mixture was washed with warm water to remove the excess of diamine. The solid was filtered and recrystallization from 70% ethanol to afford a pure product. TLC and 1H NMR analysis showed that coloured products were nearly pure. The color could be removed with activated charcoal**.**



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

Figure 3: Synthesis Scheme of Telmisartan Impurity

5. RESULTS

5.1 Physicochemical Properties

Table.1

Parameter	Result
Molecular Formula	$C_{14}H_{10}N_4$
Molecular Weight	234.256
Melting Point	310-315ºC
R_f Value	0.65
% Yield	78%

5.2 Thin Layer Chromatography (TLC)

Mobile phase: Chloroform: Methanol: Ethyl Acetate (3:2:1 v/v)

R_f Value = 0.65

5.3 IR Data[4,5]

Table 2.

Sr.No.	v (cm^{-1})	Functional group assignment
1.	3100- 3500	–NH stretching.
2.	3000-3100	Aromatic –CH stretching.
3.	1400-1600	Aromatic C=C stretching.
4.	1345	C-N- stretching.
5.	3100-3500	N-H stretching.

5.4.1 ^{1}H NMR

Table 3.

Sr. No.	Chemical shift (δ ppm)	No. of protons	Type of peak	Assignment of peak
1.	9.18	2	s	-NH of benzimidazole.
2.	7.16-7.61	8	m	Aromatic Protons.

5.4.2 ^{13}C NMR

Table 4:

Sr.No.	δ(ppm)	Carbon Assignment
1.	151.2	2C of Imidazole
2.	114.8- 139.39	12C of Phenyl

5.5 UV Method Development [4,9]

The λmax of Telmisartan impurity in methanol was found to be 279 nm.

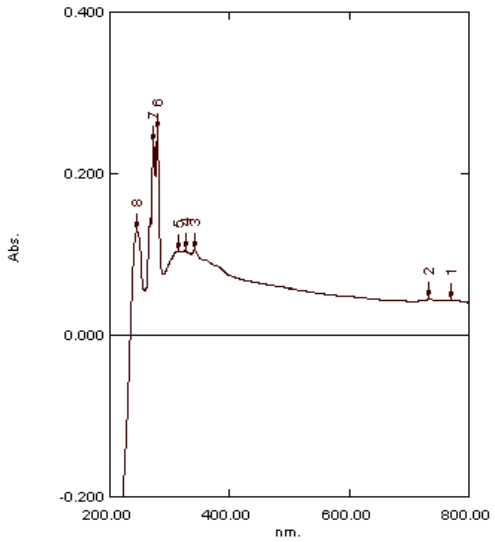


Figure 4: UV spectra of TEI

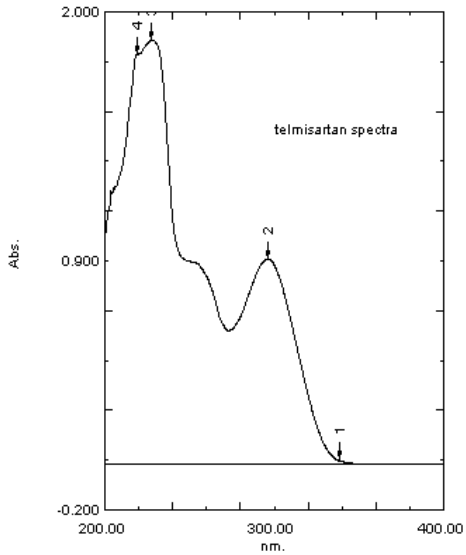


Figure 5: UV spectra of Telmisartan

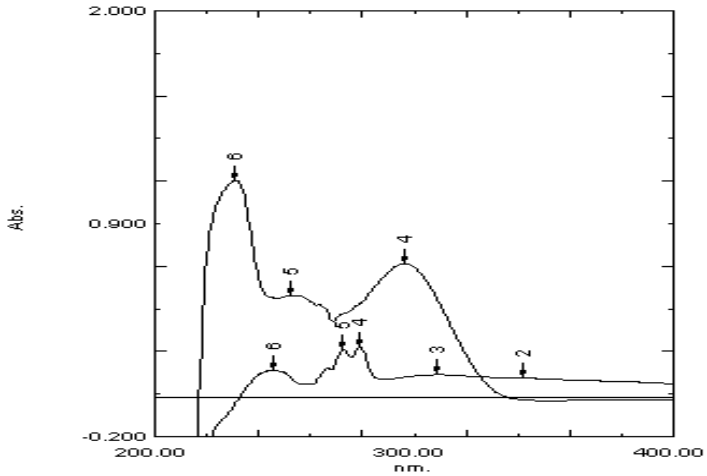


Figure 6: Overlain UV spectra of Telmisartan and Telmisartan impurity

Table 5: Linearity

Sr. No	Concentration (ppm)	Absorbance
1	10	0.1011
2	15	0.1608
3	20	0.2024
4	25	0.2530
5	30	0.3039
6	35	0.3642

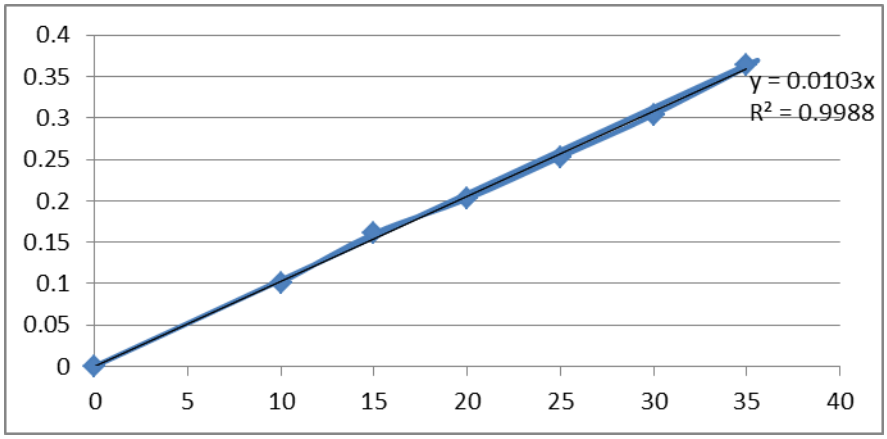


Figure 7: Calibration curve

Table 6: Intra-day Precision

Sr. No	Concentration (ppm)	Absorbance	SD	%RSD
1	25	0.2534	0.00354	1.3954
2	25	0.2504		
3	25	0.2600		
4	25	0.2511		
5	25	0.2552		
6	25	0.2520		

Table 7: Inter-day Precision

Sr. No	Concentration (ppm)	Absorbance	SD	%RSD
1	25	0.2594	0.0042	1.629
2	25	0.2587		
3	25	0.2612		
4	25	0.2501		
5	25	0.2562		
6	25	0.2612		

Table 8: Ruggedness

Sr. No	Concentration (ppm)	Analyst I	Analyst II	SD I	SD II	%RSD I	%RSD II
1	25	0.2534	0.2614	0.00354	0.00446	1.395	1.735
2	25	0.2504	0.2578				
3	25	0.2600	0.2618				
4	25	0.2511	0.2571				
5	25	0.2552	0.2540				
6	25	0.2520	0.2501				

Table 9: Robustness

Sr. No	Concentration (ppm)	Absorbance I	Absorbance II	SD I	SD II	%RSD I	%RSD II
1	25	0.2590	0.2645	0.0054	0.0044	2.0	1.67
2	25	0.2570	0.2643				
3	25	0.2683	0.2667				
4	25	0.2692	0.2653				
5	25	0.2587	0.2651				
6	25	0.2589	0.2546				

Table 10: Recovery Study

Sr. No	Drug / Formulation	Percentage recovery			Mean	SD	%RSD
		50%	100%	150%			
1	Bulk	98.45	98.90	97.96	98.43	0.4701	0.4775
2	Tablet	98.53	97.66	98.29	98.15	0.4549	0.4634

6. DISCUSSION

6.1 Linearity and Range

The given method was obtained in range of 10-100 µg/ml. The standard Calibration curve was obtained by plotting the absorbance against its concentration measured at 279 nm. The regression coefficient was found to be 0.998 and slope was found to be 0.010.

6.2 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 where all the Relative Standard Deviations were below 2%.

6.3 Ruggedness

The method was performed by changing analyst and the method was found to be rugged with standard deviation 0.0040 and relative standard deviation 1.565%.

6.4 Robustness

The robustness was performed by change in scanning speed and method was robust with standard deviation 0.0049 and relative standard deviation 1.835%.

6.5 LOD and LOQ

The LOD 1.062 and LOQ 3.54 ensure that the method is more sensitive and selective.

6.6 Accuracy and Recovery

The results within the range 97% - 99% ensure an accurate method.

7. CONCLUSION

The Process related impurity of Telmisartan in bulk and formulation was synthesized, characterized and the UV method was developed according to ICH Q2B guidelines for quantitation of 1H, 1'-H-2, 2'-Bibenzimidazole from Telmisartan bulk and tablet formulation. The synthesis of Impurity was carried out by Benzmidazole synthesis. The % yield was found to be 78%. The preliminary evaluation was done on laboratory scale viz. melting point, TLC and elemental analysis. The melting point of Impurity was found to be 310-315^{0}C. The TLC of 1H, 1'-H-2,2'-Bibenzimidazole impurity was carried by using Chloroform: Methanol: Ethyl Acetate (3:2:1) and the R_f was found to be 0.65.The confirmation of structure of 1H, 1'-H-2,2'-Bibenzimidazole was carried out by using sophisticated instruments viz, FT-IR, NMR (^{1}H and ^{13}C), A UV method was developed to identify and quantify the 1H, 1'-H-2,2'-Bibenzimidazole impurity from Telmisartan bulk and formulation, as per ICH Q2B guidelines. The method was found to be linear, precise, robust, rugged and accurate. Finally Telmisartan impurity was quantified from bulk Telmisartan and its marketed tablet formulation.

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