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Research Article

SPECTROPHOTOMETRIC METHODS FOR ESTIMATION OF TELMISARTAN BULK DRUG AND ITS DOSAGE FORM

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ABSTRACT

Telmisartan (TLM) is an angiotensin II receptor antagonist used in the treatment of hypertension. There are many spectrophotometric methods available for the determination of Telmisartan and this present paper involves three methods Method A involves adding of $KMnO_4$ Solution, Fast green FCF and Sodium Sulphate solution and we get a green colored chromogen observed at 620nm. Method B involves adding of 0.1N HCl, Napthol Blue Black reagent and Chloroform and we acquire slight blue chromogen observed at 590nm. Method C involves adding of 0.1N HCl, water and observed at 426nm.

Keywords: Telmisartan (TMS), Spectrophotometry, Validation.

INTRODUCTION

Telmisartan[1] is 4'-[1, 4'-dimethyl-2-propyl [2, 6'-bi-benzimidazole]-1'-yl] methyl 1, 1'- biphenyl 2-carboxylic acid(Fig no.1). Telmisartan is practically insoluble in water; sparingly soluble in strong acid; soluble in strong bases.[1-4] It blocks the vasoconstrictor and aldosterone secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland Literature survey revealed that there are many methods[5-10] like HPTLC, RP- HPLC and LC–MS/MS for determination of Telmisartan. The simultaneous estimation method is also available for telmisartan like HPLC. As the analysis is an important component in the formulation development of any drug molecule. It becomes essential to develop a simple, sensitive, accurate, precise, reproducible method for the estimation of drug samples.

MATERIALS AND METHODS

Apparatus

The present work was carried out on UV-VISIBLE spectrophotometer. The absorption spectra of reference and test solution were carried out in a 1 cm quartz cell over the range of 200-800nm.

Chemicals and reagents

All chemicals of analytical grade were used.

0.1M HCl: It was prepared by diluting 0.85 ml of conc.Hcl in 100 ml of distilled water.

NBB dye solution: Naphthol Blue Black (NBB) dye was prepared by dissolving 0.2g of NBB in 100ml of 0.1N NaOH. The dye solution was washed (to remove impurities) with equal volume of Chloroform and separated dye solution was used.

$KMnO_4$: It was prepared by dissolving 31.6mg in 100ml of 2M Sulphuric acid

Fast Green FCF: It was prepared by dissolving 100mg of Fast Green FCF in 100ml of 1M Sulphuric acid.

Sodium Sulphate: It was prepared by dissolving 14.2g of Sodium Sulphate in 100ml of distilled water.

0.1M Sulphuric acid: 5.2ml of Sulphuric acid was dissolved in 100ml of water.

PREPARATION OF STANDARD DRUG SOLUTION

METHOD A: A stock solution of 1mg/ml was prepared by dissolving 100mg of Telmisartan in 100ml of distilled water. This solution is diluted to obtain the required concentration (100µg/ml).

METHOD B: A stock solution of 1mg/ml was prepared by dissolving 100mg of Telmisartan in 100ml of distilled water. This solution is diluted to obtain the required concentration (100µg/ml)

METHOD C: A stock solution of 1mg/ml was prepared by dissolving 100mg of Telmisartan in 100ml of distilled water.

METHOD D: A stock solution of 1mg/ml was prepared by dissolving 100mg of Telmisartan in 100ml of distilled water.

PROCEDURE

Method A

Aliquots (0.5-3.0ml, 50µg.ml^{-1}) of standard TMS solution were taken into a series of 25ml calibrated tubes. To these tubes, 1.0ml (2x10^{-3} M) of $KMnO_4$ solution was added and the total volume in each tube was brought to 10 ml with distilled water and kept aside for 15 min at room temperature. Then 4.0ml (1.236x10^{-4} M) each of FGFCF solution and (1M) of sodium sulphate solution were added successively. After 10 min, the volume was made up to the mark with distilled water. The absorbance was measured at 625nm against distilled water. A blank experiment was carried out in a similar manner-omitting drug. The decrease in absorbance corresponding to consumed permanganate and in turn the drug concentration was obtained by subtracting the decrease in absorbance of the test solution (dye-test) from that of the blank solution (dye-blank).

Method B

Into a series of 125 ml separating funnels containing aliquots of standard TMS solution (0.5 –3.0 ml, 100µg.ml^{-1}), 6 ml of 0.1M HCl solution and 2 ml of (3.2x10^{-3}M) of NBB solution were added. The total volume of aqueous phase in each separating funnel was adjusted to 15.0ml with distilled water. To each separating funnel 10.0ml of chloroform was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated chloroform layer was measured at 580nm against a similar reagent blank within the stability period (15 min-1hour).

Method C

Into a series of 125 ml separating funnels containing aliquots of standard TMS solution (0.5 –3.0 ml, 50µg.ml^{-1}), 6 ml of buffer (pH3.5) and 2 ml of BTB, solutions were added for M_{1c}. The total volume of aqueous phase in each separating funnel, was adjusted to 15.0ml with distilled water. To each separating funnel 10.0ml of chloroform was added and the contents were shaken for 2 min. The two phases were allowed to separate and the absorbance of the separated chloroform layer was measured at 420nm against a similar reagent blank within the stability period (15 min-1hour)

Method D

Aliquots of working standard solutions of Telmisartan 1-5ml (100µg/ml) were transferred into a series of 10ml calibrated test tubes. To this 0.1N Hcl and water are added and observed spectrophotometrically at 246nm.

CHEMISTRY OF COLOURED SPECIES

METHOD A

TMS exhibits reducing property due to the presence of functional moieties vulnerable to oxidation selectively with oxidizing agents such as MnO_4^- (M_A), under controlled experimental conditions. When treated with known excess of oxidant TMS undergoes oxidation, giving products of oxidation inclusive of reduced form of oxidant besides unreacted oxidant. It is possible to estimate the drug content colorimetrically, which is equivalent to either the reacted oxidant or reduced form of oxidant formed. The unreacted oxidant can be estimated colorimetrically either by decrease in the intensity of dye color (FG FCF, M_A) due to disruption of chromophoric centres in the dye.

STEP -I

The first step in the methods mentioned above is the oxidation of TMS with the oxidant.

TMS + MnO_4^- $\rightarrow$ oxidation products + Mn II + un reacted MnO_4^- (M_A)

STEP-II

The second step concerns with the estimation of the un reacted oxidant with appropriate dye or chromogenic reagent

MnO_4^- + FGFCF → FGFCF + MnII + Mixture of compounds with rupture of conjugated system in dye reproducible,

METHOD B & C

As TMS possess tertiary nitrogen, it involves in ion association complex formation with acid dyes-NBB (M_B), BTB(M_C) which is extractable into chloroform from the aqueous phase. The protonated nitrogen (positive charge) of TMS in acid medium is expected to attract the oppositely charged part (negative charge) of the dye and behave as a single unit being held together by electrostatic attraction. Based on the analogy, the structures of ion – association complexes are shown in scheme 01.

Validation of the Proposed Methods

The validation of the developed spectrophotometric method was carried out as per the ICH guidelines (ICH Q2B 1996). According to the ICH guidelines the following parameters are evaluated [11]

Linearity

Under the optimized experimental conditions, the calibration curve for Telmisartan was constructed by analyzing a series of standard solutions of the drug. The regression equations for the results were derived by using the least squares method. For all methods, the Beers law plot was linear with very small intercept and good correlation value.

Precision

The precision of an analytical method is determined by assaying a sufficient number of aliquots of a homogeneous sample to be able to calculate statistically valid estimate of % Relative Standard Deviation (%RSD). Intermediate precision was done to express within laboratory variation, on different days. Five replicates of the working standards and sample solutions were analyzed %RSD was found to be less than %. Accuracy were determined for three methods and resulted are reported in table.

Specificity

Results of tablet solution showed that there is no interference of the excipients when compared with the working standard solution. Thus, the method was said to be specific

Accuracy

The accuracy of the proposed method was also confirmed through recovery studies using the method of standard additions. Results indicated good recoveries which reflect the selectivity of the extraction procedure for Telmisartan from the commonly encountered common excipients and additives. Therefore the proposed method can be considered specific for the determination of Telmisartan in commercially dosage forms

RESULTS AND DISCUSSION

The optimum conditions for methods A, B ,C and D have been established by varying the parameters one at a time and keeping the other parameters fixed and observing the effects of products on the absorbance of the sample and colored species. Beer'slaw limits, molar absorptivity, Sandal's sensitivity, % range of error and % relative standard deviation are summarized in Table I. The regression analysis using the method of least squares was made for the slope (b), intercept (a) and correlation coefficient (r)obtained from different concentrations are given in Table I The results showed that these methods have reasonable precision.

To evaluate the validity and reproducibility of the methods, known amounts of pure drug were added to the previously analyzed pharmaceutical dosage forms and the mixtures were analyzed by the proposed methods. The percentage recoveries are given in Table - 2. The interference studies revealed that the common excipients and other additives that are usually present in the injection dosage forms did not interfere at their regularly added levels.

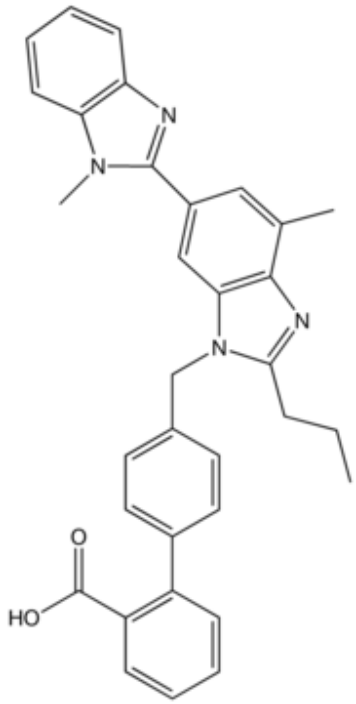
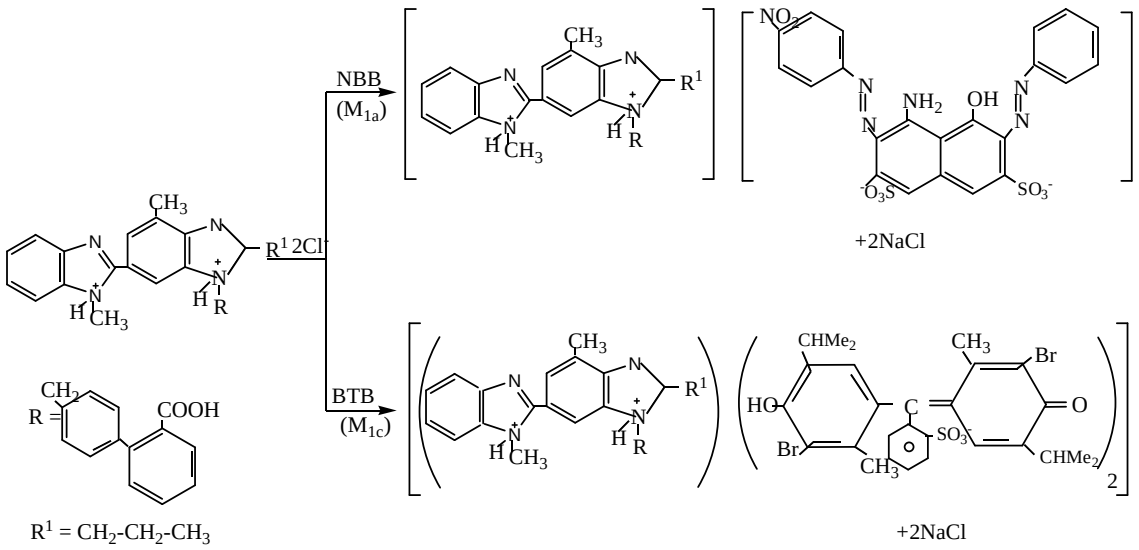


Fig. 1: Structure of Telmisartan

IUPAC NAME:

Telmisartan is 4'-[1, 4'-dimethyl-2-propyl [2, 6'- bi-benzimidazole]-1'-yl] methyl 1, 1'- biphenyl 2-carboxylic acid.



Scheme 01

Table 1: Optical regression characteristics, prcision and accuracy of the proposed methods

Parameter	NBB / M_A	BTB /M_B	$KMnO_4$/FGFCF/M_C	0.1MHCL/M_D
λ_{max} (nm)	580	420	625	246
Beer's law limits (µg/ml)	1.5-12	0.5-6.0	0.8-6.0	4-20
Detection limit (µg/ml)	0.5117	0.2215	0.0945	0.0447
Molar absorptivity (1 $mol^{-1}.cm^{-1}$)	$2.036x10^4$	$3.131x10^4$	$2.693x10^4$	$3.0105x10^4$
Sandell's sensitivity (µg.cm^{-2}/0.001 absorbance unit)	0.05414	0.04076	0.0451	0.1750
Optimum photometric range (µg/ml)	7 -95	2.8 - 4.2	3.2 -5.4	2 -12
Regression equation (Y=a+bc) slope (b)	$8.0x10^{-2}$	$1.191x10^{-1}$	$1.025x10^{-1}$	$5.5x10^{-2}$
Standard deviation on slope (S_b)	$4.114x10^{-3}$	$2.652x10^{-3}$	$1.1958x10^{-3}$	$1.6224x10^{-3}$
Intercept (a)	$2x10^{-4}$	$4.1x10^{-3}$	$2.7x10^{-3}$	$5.2007x10^{-3}$
Standard deviation on intercept (S_a)	$1.364x10^{-2}$	$8.7937x10^{-3}$	$3.2309x10^{-3}$	$4.383x10^{-3}$
Standard error on estimation (S_e)	$1.301x10^{-2}$	$8.3845x10^{-3}$	$3.78x10^{-3}$	$1.026x10^{-2}$
Correlation coefficient (r)	0.9996	0.9999	0.9999	0.9999
Relative standard deviation (%)*	0.6633	0.8544	1.277	0.7068
% Range of error (confidence limits) 0.05 level	0.6963	0.8970	1.341	0.0204
0.01 level	1.092	1.406	2.102	0.0408
% error in Bulk samples **	0.432	-0.261	-0.206	0.316

Y = a+ bx where x is the concentration of Telmisartan µg/ml and Y is the absorbance at the respective λ max.
**Average of six determinations considered.

Table 2: Assay of Telmisartan in Pharmaceutical formulation

Sample *	Amount taken (mg)	Amount found by proposed Methods**				Reference method	Percentage recovery by proposed methods***			
		M_A	M_B	M_C	M_D		M_A	M_B	M_C	M_D
Tablet I	20	19.93±0.36 F=2.25 t=0.75	19.72±0.30 F=1.56 t=0.513	19.98±0.16 F=2.25 t=1.55	19.65±0.14 F=2.93 t=1.36	19.8±0.24	100.6 ±1.8	99.59 ±1.5	100.9 ±0.8	99.24 ±0.7
Tablet II	20	19.97±0.24 F=1.19 t=0.376	19.82±0.16 F=1.89 t=0.911	20.11±0.35 F=2.53 t=1.23	19.98±0.21 F=1.097 t=0.483	19.92±0.22	100.25 ±1.2	99.49 ±0.8	100.95 ± 1.7	100.3 ±1.05
Tablet III	40	39.96±0.124 F=1.44 t=1.38	39.89±0.134 F=1.236 t=2.103	39.5±0.212 F=2.024 t=2.02	39.62±0.169 F=1.286 t=1.08	39.72±0.149	100.6 ±0.31	100.4 ±0.34	99.47 ±0.53	99.74 ±0.42
Tablet IV	40	39.5±0.284 F=3.11 t=2.023	39.06±0.12 F=1.77 t=2.22	39.41±0.205 F=1.621 t=1.635	39.11±0.112 F=2.066 t=1.667	39.24±0.161	100.6 ±1.14	99.54 ±0.3	100.43 ± 0.51	99.66 ±0.28

* Tablets from four different pharmaceutical companies.
** Average ± standard deviation of six determinations, the t-and F-test values refer to comparison of the proposed method with the reference method. Theoretical values at 95% confidence limit, F = 5.05, t = 2.57
*** Recovery of 10mg added to the preanalysed pharmaceutical formulations (average of three determinations).

CONCLUSION

The proposed spectrophotometric methods were accurate, precise and reliable for the measurement of Telmisartan in dosage form. The developed spectrophotometric method was validated for estimation of Telmisartan using linearity, range, accuracy and precision. The RSD for all parameters was found to be less than one, which indicates the validity of method and assay results obtained by this method are in fair agreement. The developed method can be used for routine quantitative estimation of Telmisartan in pharmaceutical Preparation.

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