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Telmisartan Content Determination in Pharmaceutical Dosage Forms by UV-Spectrophotometry

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Abstract **Original Research Article**

Antihypertensive effect of Telmisartan is result of it's action by specific blockage of angiotensin II receptors. The aim of current study was the application of the validated UV-spectrophotometric method for determination of Telmisartan at λ = 298 nm in 99.98 % ethanol. UV-VIS diode array spectrophotometer was used. From the homogenized tablets of Telmisartan tabl. 80 mg accurately were measured samples, containing an amount, equivalent to 80 mg Telmisartan and were dissolved to 100.0 ml with 99.98 % ethanol in volumetric flasks. From the obtained solutions, an aliquot parts of 1.0 ml were diluted separatelly with the same solvent to 100.0 ml. Data for Chauvenet's criterion are lower than maximum permissible value (U = 1.73; N = 6), which was applied for the assessment of the need for the removal of sharply different results. Analytical parameter precision was proved by the fact, that all results for the quantities in model mixtures and in tablets correspond to the relevant confidence interval: model mixtures: 80.06 mg ÷ 81.34 mg; tablets 80 mg: 77.79 mg ÷ 81.09 mg. Standard deviations were lower than 1.2; related standard deviations were lower than 1.6 % and relative errors were lower than 0.7 %. The validated method can be applied for the determination of Telmisartan in dosage drug preparations.

Keywords: Telmisartan, UV-spectrophotometry, determination, pharmaceutical dosage preparations, tablets.

INTRODUCTION

Treatment of hypertension becomes more successful by the development in recent years of a new class of chemical compounds – sartans (angiotensin II-receptor antagonists, ARA-II, C09CA as ATC classification WHO), which block specific renin-angiotensin aldosterone system [1]. Telmisartan (4′-[(1,4′-dimethyl-2′-propyl[2,6′-bi-1H-benzimidazol]-1′-yl)methyl][1,1′-biphenyl]-2-carboxylic acid) (Fig. 1.) is applied for treatment of essential hypertension [2, 3], left ventricular hypertrophy [4] and anorexia [5] and decreases in largely blood pressure than Losartan [6].

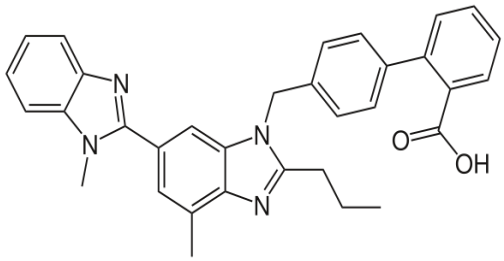

Fig-1: Chemical structure of Telmisartan

UV-spectrophotometric methods have been applied very often for the determination of different drugs in pharmaceutical dosage formulations: Methoxsalen (λmax = 247 nm) [7]; Olmesartan medoxomil (λmax = 257 nm) [8]; Ambrisentan (λmax = 263.5 nm) [9]; Aceclofenac (λmax = 273.6 nm) [10]; Bosentan (λmax = 274 nm) [11]; Lamivudine (λmax = 282 nm) [12]; Halofantrine (λmax = 290 nm) [13] and for quantification of components in combined dosage drug forms: simultaneous equation method for Ketotifen (λmax = 301 nm) and Salbutamol (λmax = 276 nm); dual wavelength method for Ketotifen (λmax

= 267.84 nm, λmax = 284 nm) and Salbutamol (λmax = 284.59 nm, λmax = 315 nm) [14].

For quantity analysis of Telmisartan in tablets have been reported the following spectrophotometric methods: 1) first derivative spectrophotometry at λmax = 241.6 nm [15]; 2) ratio derivative spectrophotometry at λmax = 242.7 nm [15]; 3) zero order spectrophotometry at λmax = 234 nm [16]; 4) difference spectrophotometry: by calculation the difference between the absorbance values of the solution in 0.01 M NaOH at λmax = 295 nm and in 0.01 M HNO_3 at λmax = 327 nm [17]; 5) spectrophotometry in visible area after derivative reaction for Telmisartan with different reagents: bromothymol blue (λ max = 412 nm) [18]; 2,5-dichloro-3,6-dihydroxy-1,4-benzoquinone (λmax = 460 nm) [19]; orange-G (λmax = 482 nm) [18]; azurin-B dye (λmax = 508 nm) [20]; eriochrome black-T (λ = 510 nm) [21], wool fat blue (λ = 585 nm) [19]; congo-red (λ = 593 nm) [22].

For Telmisartan in tablets the developed UV-spectrophotometric methods, based on the measurement of absorbance in specific solutions are in: 0.1 M NaOH [23]; 0.1 M NaOH : distilled water = 20 : 80 v/v [24]; 95 % ethanol: 0.1 M $NaHCO_3$ = 60 : 40 v/v [25]; methanol [26]; methanol : water = 90 : 10 v/v [27]; 10 M urea [28].

For the determination of Telmisartan in combinations with other drugs in dosage pharmaceutical preparations have been reported the following different analytical methods: 1) UV-spectrophotometry: Telmisartan 80 mg and Hydrochlorotiazide 12.5 mg in tablets Micardis Plus® and Pritor Plus® [29]; 2) UV-spectrophotometry: absorbance correction method: Telmisartan (λmax = 325 nm), Chlorthalidone (λmax = 225 nm) and Cilnidipine (λ = 350 nm) [30]; 3) first-derivative and ratio derivative spectrophotometry and spectrofluorimetry for the simultaneous determination of Telmisartan and Hydrochlorothiazide in pharmaceutical dosage forms [15]; 4) TLC-densitometry for the simultaneous analysis of Telmisartan and Hydrochlorothiazide in pharmaceutical dosage forms [15]; 5) Reversed Phase High Performance Liquid Chromatography (RP-HPLC): Telmisartan and Ramipril on column: ACE 5 C_{18}, 25 cm, column temperature: 30 °C, mobile phase: 0.1 mol/l sodium perchlorate : acetonitrile = 55 : 45 v/v, flow rate: 1.5 ml/min, λ = 215 nm [31]; 6) High Performance Thin-Layer Chromatography: for Telmisartan and Amlodipine besilate: stationary phase: Silicagel $G_{60}F_{254}$; mobile phase: tetrahydrofurane : dicloroethane : methanol : ammonia = 6.0 : 2.0 : 1.0 : 0.4 v/v/v/v, densitometric detection at λ = 326 nm: R_f = 0.22 (Telmisartan), R_f = 0.45 (Amlodipine besilate) [32].

The disadvantage of derivative spectrophotometry especially of the zero-crossing technique is that little differences in the wavelength setting are the reason for method non-reproducibility. The advantage of the classical UV-spectrophotometry in comparison with UV-derivative method, is the low susceptibility towards changes in the apparatus parameters [33].

The aim of current study was the application of the validated UV-spectrophotometric method for determination of Telmisartan in tablets by conventional UV-spectrophotometric method in 99.98 % ethanol at λ = 298 nm by application of method of external standard.

MATERIALS AND METHODS

- Drug products: Telmisartan tabl. 80 mg (Boehringer Ingelheim)
- Reference standard: Telmisartan (98 %) (Sigma Aldrich, N:T8949)
- Reagents with analytical grade of purity: 99.98 % ethanol (Sigma Aldrich, N: SZBD 0500 V UN 1170).

Method

UV-spectrophotometry was applied.

Equippment

UV-VIS diode array spectrophotometer (Hullett Packard N: 8452 A) was used.

Preparation of test-solutions of Telmisartan tabl. 80 mg in 99.98 % ethanol

From the homogenized tablets of Telmisartan tabl. 80 mg (with an average weight) on an analytical balance with an accuracy of 4 characters accurately were measured 6 samples, containing an amount, equivalent to 80 mg Telmisartan and were dissolved to 100.0 ml with 99.98 % ethanol in volumetric flasks. From the obtained solutions, an aliquot parts of 1.0 ml were diluted separatelly with the same solvent to 100.0 ml.

Preparation of model mixtures with reference standard Telmisartan for estimation of analytical parameter precision.

Six equal homogenous model mixtures were prepared from the most used in tablets supplement starch by adding of reference standard Telmisartan, equivalent to 80 mg – 100 % of it's concentration in tablets (80 mg). An accurately weighed quantity, equivalent to 80 mg of reference standard Telmisartan was measured on analytical balance with an accuracy of 4 characters and was dissolved to 100.0 ml with 99.98 % ethanol in volumetric flask. From this solution an aliquot part of 1.0 ml was diluted with the same solvent to 100.0 ml to obtaining solution of Telmisartan with concentration: 8.10^{-6} g/ml.

Preparation of reference solution of Telmisartan for quantity analysis of Telmisartan tabl. 80 mg by method of external standard.

An accurately weighed content, equivalent to 80 mg of reference standard Telmisartan was measured on analytical balance with an accuracy of 4 characters and was dissolved to 100.0 ml with 99.98 % ethanol in volumetric flask. From this solution an aliquot part of 1.0 ml was diluted with the same solvent to 100.0 ml. to obtaining solution of Telmisartan with concentration: 8.10^{-6} g/ml.

UV-spectrophotometric procedure

The final test-solutions of Telmisartan tabl. 80 mg, model mixtures and standard solution of Telmisartan in 99.98 % ethanol at a concentration of 8.10^{-6} g/ml were analyzed spectrophotometrically at λ = 298 nm by using as a compensation 99.98 % ethanol.

RESULTS AND DISCUSSION

Validation is a significant tool for enhancing qualities of pharmaceutical products [34]. In our previous investigation [35] the UV-spectrophotometric method for determination of Telmisartan at λ = 298 nm in 99.98 % ethanol, was validated for analytical parameters in accordance with the basic validation concepts [36] and the International Conference on Harmonization Guidelines [37]. For this study from reference standard Telmisartan were preprared 3 model mixtures for validation of UV-spectrophotometric method for determination of analytical parameters accuracy, linearity, limit of detection (LOD) and limit of quantitation (LOQ) [38].

An accurately weighed quantities, equivalent respectively to 60 mg (T_{60}), 80 mg (T_{80}), 100 mg (T_{100}) of reference standard Telmisartan were measured on analytical balance with an accuracy of 4 characters and were dissolved to 100.0 ml with 99.98 % ethanol in volumetric flask. From every solution an aliquot part of 1.0 ml was separately diluted with the same solvent to 100.0 ml., to obtaining solutions with Telmisartan concentrations respectively: 6.10^{-6} g/ml, 8.10^{-6} g/ml and 1.10^{-5} g/ml, and were analysed at λ = 298 nm against 99.98 % ethanol [35]. The experimental results were subjected to a linear regression analysis. The regression equation y = 70980. x + 0.027 (A > 2), show the proportional accordance A = f (C) in linear concentration range: 3.10^{-6} g/ml ÷ $1.25.10^{-5}$ g/ml, where the Buge – Lambert – Beere Law was valid. The obtained data for limit of detection and limit of quantitation were: LOD = $8.3.10^{-8}$ g/ml; LOQ = $2.77.10^{-7}$ g/ml. Analytical parameter accuracy is represented by the degree of recovery, which in the corresponding confidence possibility suit the confidence interval: R C_{T60}: 100.31 % ÷ 102.05 %; R C_{T80}: 99.22 % ÷ 103.18 %; R C_{T100} : 93.58 % ÷ 101.9 %.

On Table 1. are presented current results for: weighed amounts of: model mixtures (average weight = 0.48 g) with excipient starch and reference standard Telmisartan (T_{80}) and of Telmisartan 80 mg tabl. (Average weight = 0.4823 g); absorbances at λ = 298 nm of model mixtures (A T_{80}) and of solutions of Telmisartan tabl. 80 mg ($A_{Tabl.}$) (Ast = 0.58446); Chauvenet's criteria for absorbances (UA_{T80}; $UA_{Tabl.}$).

Table-1: Absorbances for Telmisartan in model mixtures and in tablets at λ = 298 nm

N :	Model mixtures with Telmisartan				Telmisartan tabl. 80 mg		
	Added T_{80}	Weighed T_{80}	A_{T80}	U A_{T80}	Weighed $_{Tabl.}$	$A_{Tabl.}$	U $A_{Tabl.}$
1.	80.33	0.4820	0.58763	1.12	0.482	0.63936	0.13
2.	80.08	0.4805	0.59521	0.78	0.488	0.66037	0.18
3.	79.72	0.4783	0.59344	0.34	0.4812	0.63489	0.09
4.	80.55	0.4833	0.5932	0.28	0.4625	0.60481	1.6
5.	81.06	0.4864	0.59544	0.84	0.4855	0.65361	0.84
6.	80.33	0.4820	0.58763	1.12	0.481	0.63759	0.46
$\overline{x}$			0.59209			0.63677	0.72
SD			0.004			0.02	
RSD [%]			0.68			3.14	

On Table 2 are summarized experimental results for: obtained by method of external standard content of Telmisartan in model mixtures (C_{T80}) and in tablets ($C_{Tabl.}$), after administration of the spectrophotometric method; degree of recovery R [%]: R C_{T80}, (R $C_{Tabl.}$); Chauvenet's criteria for obtained content of Telmisartan in model mixtures (U C_{T80}) and in tablets (U $C_{Tabl.}$); N – number of individual measurements (1 ÷ 6); $\overline{x}$ – mean arithmetic error; S $\overline{x}$ – mean square error; E [%] – relative error; P – confidence possibility: 95 %, t – coefficient of Student: 2.57.

Table-2: Content of Telmisartan in model mixtures and in tablets

	Model mixtures with Telmisartan			Telmisartan tabl. 80 mg		
N:	C_{T80} [mg]	R C_{T80} [%]	U C_{T80}	C_{Tabl} [mg]	R C_{Tabl} [%]	U C_{Tabl}
1.	80.1	99.71	0.97	79.75	99.31	0.26
2.	81.39	101.64	1.11	81.05	101.31	1.35
3.	81.52	102.26	1.32	79.02	98.78	0.35
4.	80.64	100.11	0.1	78.32	97.9	0.94
5.	80.43	99.22	0.44	80.63	100.79	1.0
6.	80.10	99.71	0.97	78.15	97.69	1.08
$\overline{\overline{X}}$ ± SD	80.7 ± 0.62			79.44 ± 1.19		
$\overline{\overline{R}}$ [%] ± RSD[%]		100.44 ± 1.21			99.7 ± 1.49	
SD	0.62	1.22		1.19	1.49	
RSD [%]	0.77	1.21		1.5	1.5	
$S_{\overline{\overline{X}}}$	0.25	0.5		0.49	0.61	
P [%]	2.57	4.03		3.37	3.37	
t	95.0	98.0		98.0	98.0	
$t.S_{\overline{\overline{X}}}$	0.64	2.02		1.65	2.06	
$\overline{\overline{X}} - t.S_{\overline{\overline{X}}}$ ÷ $\overline{\overline{X}} + t.S_{\overline{\overline{X}}}$	80.06 ÷ 81.34	98.42 ÷ 102.46		77.79 ÷ 81.09	97.24 ÷ 101.36	
E [%]	0.31	0.5		0.62	0.61	

Data for Chauvenet's criteria for absobances and for obtained by method of external standard content of Telmisartan in model mixtures and in tablets are lower than maximum permissible value (U = 1.73; N = 6), which was applied for the assessment of the need for the removal of sharply different results.

The analytical parameter precision (repeatability) for model mixtures with reference standard Telmisartan and for Telmisartan tablets, was characterized by uncertainty of the result, which is determined by: standard deviation SD, related standard deviation RSD and confidence interval ($\overline{\overline{X}} \pm t.S_{\overline{\overline{X}}}$), as per ICH guidelines [37]. All of the experimental data correspond to the respective confidence intervals at the corresponding confidence probability.Standard deviations are lower than 1.2; related standard deviations are lower than 1.6 % and relative errors are lower than 0.7 %.

CONCLUSION

Validated UV-spectrophotometric method for determination of Telmisartan in pharmaceutical dosage preparations (tablets) by the external standard method at λmax = 298 nm was applied. All of the experimental data correspond to the respective confidence intervals at the corresponding confidence probability. Precision was proved by the fact that all results for the quantities in model mixtures and in tablets correspond to the relevant confidence interval: model mixtures: 80.06 mg ÷ 81.34 mg; tablet's 80 mg: 77.79 mg ÷ 81.09 mg. The validated method can be applied for the determination of Telmisartan in dosage drug preparations.

List of symbols and abbreviations

A – Absorbance
C – concentration
C_{L40} – 40 mg Losartan Potassium
C_{L50} – 50 mg Losartan Potassium
$C_{L62.5}$ – 62.5 mg Losartan Potassium
E [%] – relative error
λ – Analytical wavelenght
N – number of individual measurements
P – confidence possibility
R – degree of recovery
RP-HPLC – Reversed Phase High Performance Liquid Chromatography
RSD – related standard deviation
SD – standard deviation
$S_{\overline{X}}$ – Mean square error
t – Coefficient of Student
$\overline{\overline{X}}$ – mean arithmetic error
$\overline{\overline{X}} \pm t.S_{\overline{\overline{X}}}$ – confidence interval
UV – ultraviolet

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