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Telmisartan quality control by validation of UV-spectrophotometric method

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Abstract

The aim of current study was to validate spectrophotometric method with UV-detection for identification and determination of Telmisartan in 99.8 % ethanol in respect of analytical parameters: selectivity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy and precision (repeatability). For Telmisartan in 99.8 % ethanol at λ max = 298 nm for $A^{1\%}_{1cm}$ and ε the obtained results for A > 0.2 and A < 0.2 are:

1) A > 0.2: at 3.10^{-6} g/ml ÷ $1.25.10^{-5}$ g/ml; $A^{1\%}_{1cm}$: 725 ÷ 823; ε: 37347 ÷ 42335
2) A < 0.2: at $2.5.10^{-7}$ g/ml ÷ 1.10^{-6} g/ml; $A^{1\%}_{1cm}$: 1201 ÷ 1567; ε: 61816 ÷ 80651

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 %. For precision is proved that all results for the quantities correspond to the relevant confidence interval: C_{T60}: 60.31 mg ÷ 60.77 mg; C_{T80}: 79.82 mg ÷ 82.18 mg; C_{T100}: 94.22 mg ÷ 101.58 mg.

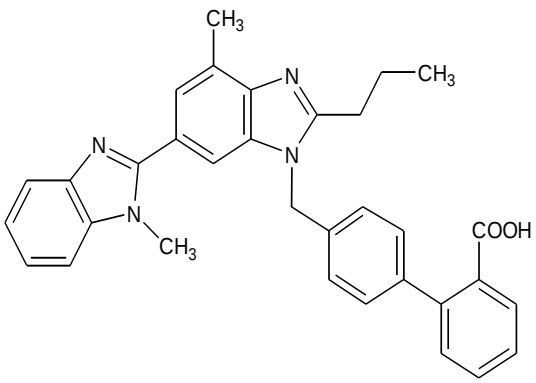
Keywords: *Telmisartan, UV-spectrophotometry, validation, linearity.*

1. Introduction

Arterial hypertension is an important widespread social disease [1]. Treatment of hypertension becomes successfully by the application of the developed in recent years a new class of chemical compounds – angiotensin II receptor antagonists (sartans) [2].

Telmisartan (4-((2-n-propyl-4-methyl-6-(1-methy-lbenzimidazol-2-yl)-benzimidazol-1-yl) methyl)-biphenyl-2-carboxylic acid) (Fig. 1.) is applied for theatment of high blood pressure alone [3] or in combinations with other antihypertensive drugs: diuretic Hydrochlorothiazide [4] and calcium blocker Amlodipine [5].

Fig. 1. Chemical structure of Telmisartan



For the determination of Telmisartan in monocomponent pharmaceutical dosage forms are described the following different methods [6]:

1) High performance liquid chromatography (HPLC) with ultraviolet and mass detection [6]

2) Thin layer chromatography-densitometry [7]

3) High performance thin layer chromatography (HPTLC) [8, 9]

4) Spectrophotometry [6, 7]

5) Spectrofluorimetry: λexcitation = 366 nm and λemission = 475 nm [7, 10]

6) Electrochemical methods: linear sweep polarography by dripping mercury electrode [11]; square-wave adsorptive stripping voltammetry by hanging mercury drop electrode [12]; cathodic adsorptive stripping voltammetry [13] and cyclic voltammetry [13].

The most applied method for quantification of Telmisartan in tablets is reversed phase (RP) HPLC with UV-detection [14]–[24] at the following different chromato-graphic conditions:

1. λ = 229 nm, C_8 column, ambient temperature, mobile phase: phosphate buffer : acetonitrile = 40 : 60 v/v, flow rate: 0.9 ml/min. [14]
2. λ = 225 nm, C_{18} column, ambient temperature, mobile phase: methanol : water = 80 : 20 v/v, flow rate: 1.0 ml/min. [15]
3. λ = 230 nm, C_{18} column (250 mm x 4.6 mm, 5 µm), mobile phase: methanol : acetonitrile = 30 : 70 v/v, flow rate: 1 ml/min. [16]
4. λ = 230 nm, C_{18} Waters column (250 mm x 4.6 mm, 5 µm), gradient mobile phase: 10 mM potassium dihydrogen phosphate: acetonitrile = 64 : 40 v/v, flow rate: 1.0 ml/min. [17]
5. λ = 230 nm, X Terra column (150 mm x 4.6 mm, 3.5 µm), mobile phase: methanol : phosphate buffer = 60 : 40 v/v, flow rate: 0.5 ml/min. [18]
6. λ = 243 nm, C_{18} column (250 mm x 4.6 mm, 5 µm), column temperature 45 ºC, mobile phase: potassium dihydrogen phosphate : acetonitrile = 60 : 40 v/v, flow rate: 1 ml/min. [19]
7. λ = 254 nm, C_{16} Supelco Discovery RP Amide column (250 mm x 4.6 mm, 5 µm), isocratic mobile phase: potassium phosphate buffer : acetonitrile = 55 : 45 v/v, flow rate: 1 ml/min. [20]
8. λ = 256 nm, Chromosil column, mobile phase: methanol : orthophosphoric acid : acetonitrile = 80 : 5 : 15 v/v, flow rate: 1.5 ml/min. [21]
9. λ = 272 nm, X Terra C_{18} column (150 mm x 4.6 mm, 5 µm), isocratic mobile phase: 20 mM potassium dihydrogen phosphate : acetonitrile = 40 : 60 v/v, flow rate: 0.8 ml/min. [22]
10. λ = 295 nm, Luna C_1 column, mobile phase: phosphate buffer : acetonitrile = 60 : 40 v/v, flow rate: 1 ml/min. [23]
11. λ = 296 nm, Phenomenex column, mobile phase: 10 mM potassium dihydrogen phosphate buffer: methanol = 20:80 v/v, flow rate: 0.8 ml/min. [24].

Ultra High Performance Liquid Chromatographic method (RP-UHPLC) has been developed for the estimation of Telmisartan in pharmaceutical dosage form by using of chromatographic system: λ = 290 nm, C_{18} Waters Aquity BEH column (100 mm x 2.1 mm, 1.7 µ), gradient mode: A mobile phase: 10 mM ammonium acetate : acetonitrile in the ratio 90 : 10 v/v; and B mobile phase: acetonitrile, flow rate: 0.3 ml/min. [25]. In other reported RP-UHPLC method Telmisartan is assayed at λ = 290 nm with a Poroshell 120EC-C_{18} column (50 mm x 4.6 mm, 2.7 µm), column

temperature: 25 ^{o}C, mobile phase: acetonitrile: 50 mM ammonium acetate buffer = 45: 55 v/v, flow rate: 0.5 ml/min. [26].

For quantity analysis of Telmisartan in tablets are reported the following spectrophotometric methods:

I) UV-spectrophotometry, based on the measurement of absorbance at:
   1) λ = 234 nm in 0.1 N NaOH : distilled water = 20 : 80 v/v [27]; 2) λ = 234 nm in 0.1 N NaOH [28]; 3) λ = 240 nm in 95 % ethanol : 0.1 N $NaHCO_3$ = 60 : 40 v/v [29]; 4) λ = 295 nm in 0.1 N NaOH [30]; 5) λ = 295 nm in methanol [31]; 6) λ = 298 nm in methanol : water = 90 : 10 v/v [32]; 7) λ = 315 nm in 10 M urea [33]

II) First derivative spectrophotometry at λ = 241.6 nm [7]

III) Ratio derivative spectrophotometry at λ = 242.7 nm [7]

IV) Zero order spectrophotometry at λ = 234 nm [28]

V) Difference spectrophotometry: by calculation the difference between the absorbance values of the solution in 0.01 M NaOH at λ = 295 nm and in 0.01 N HNO_3 at λ = 327 nm [34]

VI) Spectrophotometry in visible area after derivatative reaction for Telmisartan with different reagents: bromothymol blue (λ = 412 nm) [35]; 2, 5-dichloro, 3, 6-dihydroxy, 1, 4-benzoquinone (λ = 460 nm) [36]; orange-G. (λ = 482 nm) [35]; azurin-B dye (λ = 508 nm) [37]; eriochrome black-T (λ = 510 nm) [38], wool fat blue (λ = 585 nm) [36]; congo-red (λ = 593 nm) [39].

For Telmisartan in tablets the reported UV-spectrophotometric methods are based on the measurement of absorbance in 0.1 N NaOH: distilled water = 20: 80 v/v [27], 0.1 N NaOH [28, 30]; 95 % ethanol: 0.1 N $NaHCO_3$ = 60:40 v/v [29], methanol [31], methanol: water = 90:10 v/v [32] and 10 M urea [33].

The aim of current study was the determination of Telmisartan in dosage preparations by UV-spectrophoto-metry in 99.8 % ethanol.

MATERIALS

I. Reference standard: Telmisartan
II. Reagents: 99.8 % ethanol

METHODS - UV-spectrophotometry

I. Preparation of solutions of reference standard Telmisartan in 99.8 % ethanol for validation of analytical parameter linearity.

An accurately weighed quantity of reference standard Telmisartan: 125 mg, 100 mg, 90 mg, 80 mg, 50 mg, 40 mg, 30 mg, 10 mg, 5 mg, 2.5 mg was dissolved in 99.8 % ethanol in a volumetric flask of 100.0 ml. An aliquot part of 1.0 ml from all of the obtained samples was diluted with with the same solvent to 100.0 ml.

The resulting solutions have a concentration of Telmisartan respectively: $1.25.10^{-5}$ g/ml; 1.10^{-5} g/ml; 9.10^{-6} g/ml; 8.10^{-6} g/ml; 5.10^{-6} g/ml; 4.10^{-6} g/ml; 3.10^{-6} g/ml; 1.10^{-6} g/ml; 5.10^{-7} g/ml; $2.5.10^{-7}$ g/ml and were analysed at λ = 298 nm against 99.8 % ethanol.

II. Preparation of solutions of reference standard Telmisartan for the validation of the method in terms of analytical parameters accuracy and precision (repeatability).

An accurately weighed quantity of reference standard Telmisartan: 60 mg, 80 mg and 100 mg was dissolved in 99.8 % ethanol in volumetric flasks 100.0 ml. Aliquot parts of 1.0 ml of these solutions are diluted with the same 99.8 % ethanol to 100.0 ml to obtain solutions with concentration of Telmisartan respectively: 6.10^{-6} g/ml; 8.10^{-6} g/ml; 1.10^{-5} g/ml.

The absorbances of last solutions were measured at λmax = 298 nm, using as blank solution 99.8 % ethanol.

III. Preparation of model mixtures of reference standard Telmisartan for validation of the method in terms of analytical parameters accuracy and precision (repeatability).

Three equal homogenous model mixtures were prepared from the most used in tablets supplement starch by adding of reference standard Telmisartan, equivalent to: 75 %: 60 mg (T60), 100 %: 80 mg (T80), 125 %: 100 mg (T100) of its concentration in tablets (80 mg).

For every mixtire were prepared 3 samples and were dissolved in 99.8 % ethanol in volumetric flasks of 100.0 ml. Aliquot parts of 1.0 ml of every of 9 resulting solutions were diluted with the same solvent to 100.0 ml.

Every sample was analysed separately by UV-spectrophotometric method by measuring of the absorbance at λ = 298 nm, using as blank solution 99.8 % ethanol.

RESULTS AND DISCUSSION

I. Estimation of specific ($A^{1\%}_{1cm}$) and molar (ε) absorbances of solutions of reference standard Telmisartan in 99.8 % ethanol at λmax = 298 nm.

Data for the values of specific ($A^{1\%}_{1cm}$) and molar (ε) absorbances of solutions of reference standard Telmisartan in 99.8 % ethanol at λmax = 298 nm in concentration interval $2.5.10^{-7}$ g/ml ÷ $1.25.10^{-5}$ g/ml were calculated and presented on Table 1.

Table 1. Specific ($A^{1\%}_{1cm}$) and molar (ε) absorbances of reference standard Telmisartan λ = 298 nm.

C [g/100 ml]	A	$A^{1\%}_{1cm}$	C [mol/l]	ε
$2.5.10^{-5}$	0.03918	1567	$4.85.10^{-7}$	80651
5.10^{-5}	0.06985	1397	$9.71.10^{-7}$	71892
1.10^{-6}	0.12012	1201	$1.94.10^{-6}$	61816
3.10^{-4}	0.23885	796	$5.83.10^{-6}$	40972
4.10^{-4}	0.32906	823	$7.77.10^{-6}$	42335
5.10^{-4}	0.36391	728	$9.72.10^{-6}$	37455
8.10^{-4}	0.58446	731	$1.55.10^{-5}$	37597
9.10^{-4}	0.65706	730	$1.75.10^{-5}$	37570
1.10^{-3}	0.76378	764	$1.94.10^{-5}$	39305
$1.25.10^{-3}$	0.90715	725	$2.43.10^{-5}$	37347

II. Validation of UV-spectrophotometric method for the analytical parameters: selectivity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision (repeatability) [41].

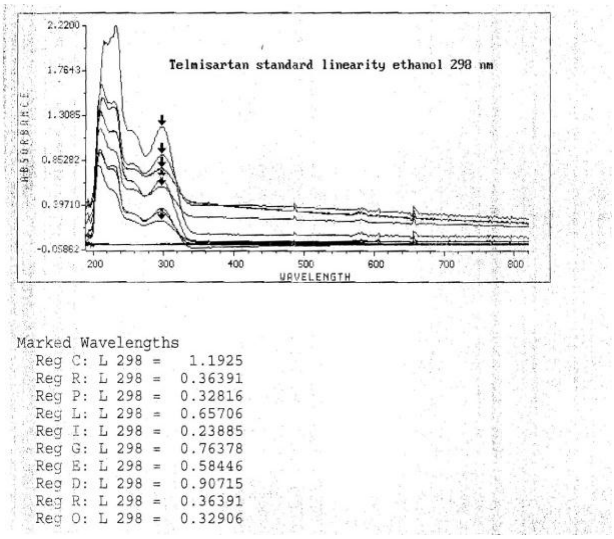
1) Selectivity

For the estimatiton of analytical parameter selectivity in the same manner like solutions of reference standard Telmisartan, "placebo" solution was prepared. In "Placebo" solution was included the used in tablets supplement starch without the active ingredient Telmartan. UV-spectrophotometric method was applied for "placebo" solution. The obtained experimental results demonstrated that in UV-spectra of "placebo" solution was not observed the measured absorption at the specific for Telmisartan wavelength λ = 298 nm. By this fact the selectivity of the proposed UV-spectrophotometric method was proved.

2) Linearity: application of method of linear regression analysis.

On Fig. 2. Are illustrated spectra of solutions of reference standard Telmisartan in 99.8 % ethanol

Fig. 2. Spectra of solutions of reference standard Telmisartan in 99.8 % – estimation of analytical parameter linearity



Linearity is the range within the signal from the detector remains in linear dependency from the concentration of analyte [40]. For the estimation of analytical parameter linearity for Telmisartan for absorbance values: A > 0.2 and A < 0.2, was searched the dependence of absorbance from concentration at the absorption maximum λ max = 298 nm. For this purpose from reference standard Telmisartan were prepared a series of solutions with decreasing concentrations and were analyzed by the written UV-spectrophotometric method. For every concentration (C) in g/ml the respective value of the absorbance (A) in absorption units (AU) at λmax = 298 nm was measured. The experimental results were subjected to a linear regression analysis. The presented regression equations: y = a.x + b are: y = 70980. x + 0.02 for A > 0.2 and y = 106866.x + 0.014 for A < 0.2 and show the proportional accordance A = f (C) in linear concentration ranges: 1.10^{-6} g/ml ÷ $2.7.10^{-5}$ g/ml for A > 0.2 and 1.10^{-6} g/ml ÷ $2.5.10^{-7}$ g/ml for A < 0.2, where the Buge-Lambert-Beere law is valid. The correlation coefficients R^2 were calculated. Parameter linearity, respectively at A > 2 and A < 0.2 is illustrated by the calibration curves, which are shown on Fig. 3. (A > 0.2) and Fig. 4. (A < 0.2.).

Fig. 3. Linearity for Telmisartan in 99.8 % ethanol for A > 0.2.

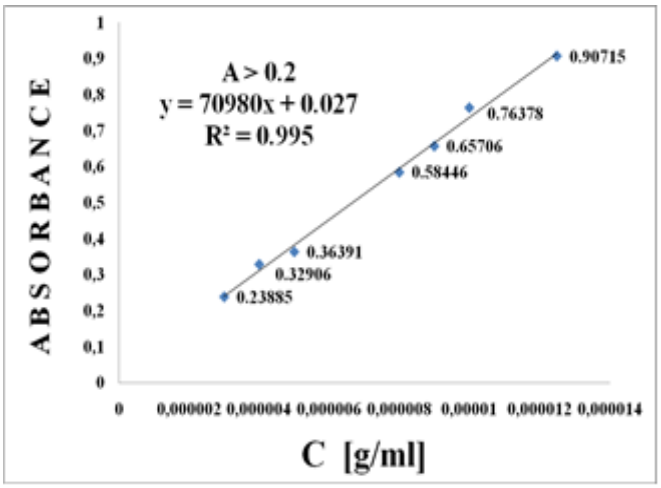
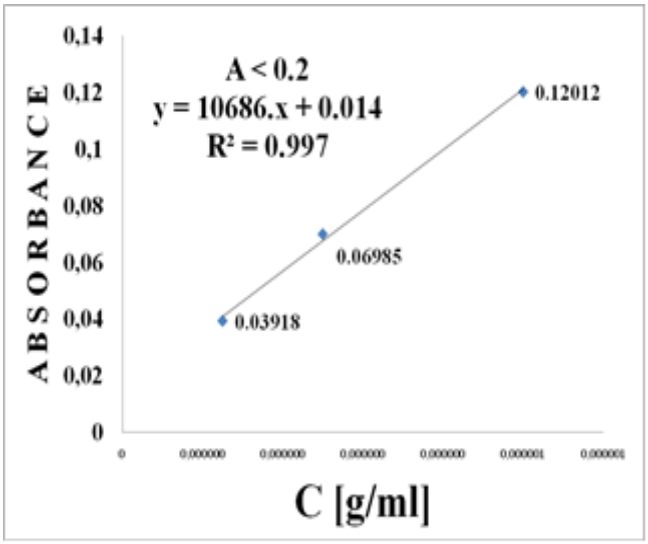


Fig. 4. Linearity for Telmisartan in 99.8 % ethanol for A < 0.2.



On Table 2. Are inclused parameters of regression equations for Telmisartan for A > 0.2 and A < 0.2, where: λ max [nm] – absorbance maximum; C [g/ml] – concentration range; y = a.x + b – regression equation; R^2 – coefficient of linear regression.

Table 2. Parameters of regression equstions for Telmisartan.

N:	Parameters	A > 0.2	A < 0.2
1.	λ max (nm)	298	298
2.	Linear range(g/ml)	$1.10^{-6} \div 2.7.10^{-5}$	$1.10^{-6} \div 2.5.10^{-7}$
3.	Regression equation	70980.x + 0.02	106866.x + 0.014
4.	Slope (a)	70980	106866
6.	Intersept (b)	0.02	0.014
7.	Correlation coefficient (R^2)	0.9956	0.9974

3) Limit of detection (LOD) and limit of quantitation (LOQ).

For the estimation of analytical parameters limit detection (LOD) and limit of quantitation (LOQ), the received at the absorption maximum λmax = 298 nm experimental results for absorbance values A < 0.2, are subjected to linear regression analysis. LOD [g/ml] and LOQ [g/ml] are based on regression equation by application of the method RMSE – root mean square error (Table. 3). In this methid for the determination of LOD and LOQ, from the regression equation 106866. x + 0.014 are calculated the predicted absorbances (Ap). For each sample were calcuated defined error $E = |A_p - A|$, $E^2 = [|A_p - A|]^2$, $E1 = \frac{\sum E^2}{n-2}$; $RMSE = \sqrt{E1}$; LOD = 3.RMSE/a; LOQ = 10.RMSE/a (Table 3.) [40].

Table 3. RMSE-method for LOD и LOQ for Telmisartan at A < 0.2.

C [g/ml]	A	Ap	| A – Ap |	$E^2 = [\|A_p - A\|]^2$
1.10^{-6}	0.12012	0.12087	0.00075	$5.62.10^{-7}$
5.10^{-7}	0.06985	0.06743	0.00242	$5.86.10^{-6}$
$2.5.10^{-7}$	0.03918	0.04072	0.00154	$2.37.10^{-6}$
$E1 = \frac{\sum E^2}{n-2}$	$8.79.10^{-6}$			
$RMSE = \sqrt{E1}$	$2.96.10^{-3}$			
LOD	$8.3.10^{-8}$ g/ml			
LOQ	$2.77.10^{-7}$ g/ml			

4) Accuracy

Analytical parameter accuracy is the degree of correspondence between the obtained average result of repeated analysis and the actual value [40].

On Table 4. Are presented data for added content of reference standard Telmisartan in 3 samples for 3 model mixtures: T60 (60 mg, 75 %) (Average weight = 0.36 g); T80 (80 mg, 100 %) (Average weight = 0.48 g); T100 (100 mg, 125 %) (Average weight = 0.6 g).

Table. 4. Added content of reference standard Telmisartan in model mixtures.

Added T60 [mg]	Weighed T60 [g]	Added T80 [mg]	Weighed T80 [g]	AddeT100 [mg]	Weighed T100 [g]
60.25	0.3615	80.33	0.482	99.8	0.5988
60.06	0.3604	80.08	0.4805	100.2	0.6012
59.77	0.3586	79.72	0.4783	100.5	0.603

On Table. 5. Are included the results for absorbances at λ = 298 nm of model mixtures of reference standard Telmisartan in 99.8 % ethanol: A_{T60} (Ast = 0.42795); A_{T80} (Ast = 0.58446); A_{T100} (Ast = 0.76378) and Chauvenet's criterion for absorbances: U A_{T60}, U A_{T80}, U A_{T100}.

Table. 5. Absorbances and Chauvenet's criterion for absorbances at λ = 298 nm of model mixtures with Telmisartan in 99.8 % ethanol.

N :	A_{T60}	U A_{T60}	A_{T80}	U A_{T80}	A_{T100}	U A_{T100}
1.	0.43401	1.01	0.58763	1.12	0.76794	1.19
2.	0.43103	0.48	0.59521	0.78	0.73941	0.59
3.	0.43092	0.54	0.59344	0.34	0. 73935	0.6
$\overline{X}$	0.43199		0.59209		0.74890	
SD	0.002		0.004		0.02	
RSD [%]	0.46		0.68		2.14	

For the estimation of accuracy of model mixtures with reference standard Telmisartan in 99.8 % ethanol are presented the results for: obtained content of Telmisartan: C_{T60}, C_{T80}, C_{T100}, after application of UV-spectrophotometric method (Table 6.), degree of recovery: R C_{T60}; R C_{T80}; R C_{T100} (Table 7.) $\overline{\overline{X}}$ – mean arithmetic error; SD – standard deviation; RSD – relative standard deviation (%); S $\overline{\overline{X}}$ – mean square error; $\overline{\overline{X}} \pm$ t.S $\overline{\overline{X}} = \overline{\overline{X}} -$ t.S $\overline{\overline{X}} \div \overline{\overline{X}} +$ t.S $\overline{\overline{X}}$ – confidence interval; E (%) – relative error. P – Confidence possibility is 95 % and t – coefficient of Student is 2.57.

Table. 6. Obtained content of Telmisartan in model mixtures.

N:	C_{T60} [mg]	C_{T80} [mg]	C_{T100} [mg]
1.	60.6	80.1	100.75
2.	60.36	81.39	96.62
3.	60.65	81.52	96.32
$\overline{\overline{X}}$ ± SD	60.54 ±0.16	81.0 ±0.79	97.90 ±2.48
SD	0.16	0.79	2.48
RSD [%]	0.26	0.98	2.53
S $\overline{\overline{X}}$	0.09	0.46	1.43
t.S $\overline{\overline{X}}$	0.23	1.18	3.68
$\overline{\overline{X}} \pm$ t.S $\overline{\overline{X}}$	60.31 ÷60.77	79.82 ÷82.18	94.22 ÷101.58
E [%]	0.15	0.57	1.46

Table. 7. Degree of recovery for Telmisartan in model mixtures.

N:	R C_{T60}[%]	R C_{T80}[%]	R C_{T100}[%]
1.	101.58	99.71	100.95
2.	100.5	101.64	96.43
3.	101.47	102.26	95.84
$\overline{\overline{X}}$ ± SD			
$\overline{\overline{R}}$ [%] ± RSD [%]	101.18 ± 0.58	101.2 ±1.31	97.74 ±2.86
SD	0.59	1.33	2.8
RSD [%]	0.58	1.31	2.86
S $\overline{\overline{X}}$	0.34	0.77	1.62
t.S $\overline{\overline{X}}$	0.87	1.98	4.16
$\overline{\overline{X}}$ ± t.S $\overline{\overline{X}}$	100.31 ÷102.05	99.22 ÷103.18	93.58 ÷101.9
E [%]	0.86	0.76	1.66

For the assessment of the need for the removal of sharply differing data is used the criterion of Chauvent. The obtained data for Chauvenet's criterion for absorbanses (Table 5.) and for the quantities (Table 6.) for Telmisartan are lower than the maximum permissible value for this criterion (U = 1.68; N = 3). By this fact is demonstrated that the results correspond to the requirements for the criterion in the analysis of 3 samples and there is no need to remove any of the received data [40].

Analytical parameter accuracy for UV-method was established by the degree of recovery at 75 % (60 mg) 100 % (80 mg); 125 % (100 mg) of the test concentration as per ICH guidelines [41]. The recovery study was performed 3 times at each level. Accuracy is represented by the degree of recovery R [%] ± RSD (%): R C_{T60}: 101.18 % ± 0.58 %; R C_{T80}: 101.2 % ± 1.31 % R C_{T100}: 97.74 % ± 2.86 %. The results show that at the used confidence possibility all experimental data for R correspond to the respective interval: R C_{T60}: 100.31 % ÷ 102.05 %; R C_{T80}: 99.22 % ÷ 103.18 %; R C_{T100}: 93.58 % ÷ 101.9 %.

5) Precision (Repeatability)

By an analytical parameter precision (repeatability) is expressed the degree of closenest of the results of measurements of one and the same value (absorbance) in the analysis of samples taken from one homogeneous sample at applcation of the same methodology at wthe same conditions for a short time [41]. Repeatability is characterized by the uncertainty of the result, which includes standard deviation (SD), relative standard deviation (RSD) and confidential interval ($\overline{\overline{X}}$ ± t.S $\overline{\overline{X}}$ = $\overline{\overline{X}}$ – t.S $\overline{\overline{X}}$ ÷ $\overline{\overline{X}}$ + t.S $\overline{\overline{X}}$). For model mixtures is proved that at the corresponding confidence possibility, all results for the obtained quantities of Telmisartan (Table 6.) in 99.8 % ethanol from the analysis of three samples from each of the three model mixtures, suit the appropriate confidence interval [40]: C_{T60}: 60.31 mg ÷ 60.77 mg (SD = 0.16; RSD = 0.26); C_{T80}: 79.82 mg ÷ 82.18 mg (SD = 0.79; RSD = 0.98); C_{T100}: 94.22 mg ÷101.58 mg (SD = 2.48; RSD = 2.53).

CONCLUSION

For Telmisartan in 99.8 % ethanol at λ max = 298 nm for $A^{1\%}_{1cm}$ and ε the obtained results for A > 0.2 and A < 0.2 are:1) A > 0.2: at 3.10^{-6} g/ml ÷ $1.25.10^{-5}$ g/ml; $A^{1\%}_{1cm}$: 725 ÷ 823; ε: 37347 ÷ 42335; 2) A < 0.2: at $2.5.10^{-7}$ g/ml ÷ 1.10^{-6} g/ml; $A^{1\%}_{1cm}$: 1201 ÷ 1567; ε: 61816 ÷ 80651. UV-spectrophotometric method for determination of Telmisartan in 99.8% ethanol at λmax = 298 nm by method of external standard is validated by the analytical parameters: selectivity, linearity, LOD, LOQ, accuracy, precision. Accuracy is represented by the degree of recovery, which suit in confidence interval: R C_{T60}: 100.31 ÷ 102.05; R C_{T80}: 99.22 ÷ 103.18; R C_{T100}: 93.58 ÷ 101.9. For precision is proved that all results for the quantities suit relevant interval: C_{T60}: 60.31 mg ÷ 60.77 mg; C_{T80}: 79.82 mg ÷ 82.18 mg; C_{T100}: 94.22 mg ÷ 101.58 mg.

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