QUANTIFICATION OF VALSARTAN IN TABLETS BY VALIDATED UV-SPECTROPHOTOMETRIC METHOD

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Abstract.

Angiotensin receptor blocker Valsartan is approved for treatment of I and II stage of hypertension. The aim of current study was the application of the validated UV-spectrophotometric method for determination of Valsartan by the external standard method in pharmaceutical dosage preparations (tablets) in 99.98 % ethanol at λmax = 252 nm and in methanol at λmax = 250 nm. UV-VIS diode array spectrophotometer was used.

Data for Chauvenet's criterion are lower than maximum permissible value (U = 1.73; N = 6), which is applied for the assessment of the need for the removal of sharply different results. All of the experimental results suit the respective confidence intervals. The analytical parameter repeatability for tablets is characterized by the uncertainty of the result, which includes standard deviation, relative standard deviation and confidential interval. All of the experimental results correspond to the respective confidence intervals at the confidence probability 98 %: Valsartan 160 mg tabl. (99.98 % ethanol): 159.69 mg ÷ 160.37 mg; Valsartan 160 mg tabl. (methanol): 158.51 mg ÷ 160.73 mg. Relative error is lower than 0.25 %.

The validated method can be applied for the determination of Valsartan in pharmaceutical dosage forms.

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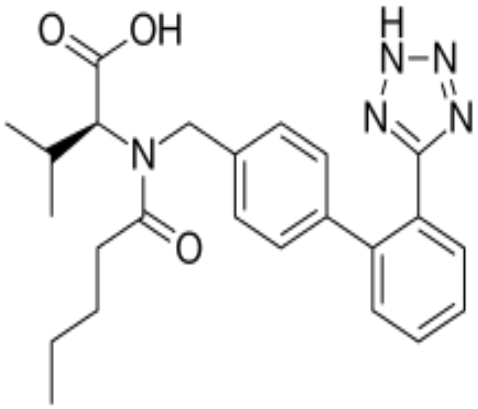
Key words: Valsartan, UV-spectrophotometry, tablets, determination.

Introduction.

Angiotensin receptor blocker Valsartan (N-(1-oxopentyl)-N-[[2prime-(1H-tetrazol-5-yl)[1,1prime-biphenyl]-4-yl]methyl]-L-valine-N-[p-(o-1H-tetrazol-5-ylphenyl)benzyl]-N-valeryl-L-valine) (**Fig. 1.**) is approved for: 1) treatment of I and II stage of hypertension [1-3], metabolic syndrome [4] and chronic heart failute [5]; 2) prevention of heart attack [6] and miocardial infarction [7]; 3) therapy of myocardial fibrosis [6], diastolic dysfunction in heart failure [6], left ventricular systolic dysfunction [8, 9], left ventricular hypertrophy [10], acute coronary syndrome [11] and acute cardiac ischemia [12].

Fig. 1. Chemical structure of Valsartan.



Spectrophotometry, gas chromatography and thin layer chromatography very often have been applied for different analysis: spectrophotometric quantification afrer derivative reactions: fluoride with alizarin red (λ = 624 nm) [13]; cobalt (II) with 2-hydroxy-5-iodothiophenol (λ = 598 nm) [14]; iron (III) with 5-(p-hydroxybenzylidene)-thiazolidone-2,4 (λ = 540 nm) [15]; cromium (VI) [16] and tantalum (V) (λ = 490 nm) [17] with hydroxythiophenol; spectrophotometry for Curcuminoid analogues [18]; investigation of organochlorine pesticides in cocoa beans by GC [19]; TLC for leave extract of *Dendranthema indicum* [20]; stem bark extract of *Psorospermum senegalense* [21].

Valsartan in tablets has been determined with second detivative UV-spectrophotometry [22]. UV-spectrophotometric methods have been developed for the simultaneous estimation of Valsartan and Hydrochlorothiazide in tablet dosage forms: I) ratio spectra derivative; II) inverse least squares techniques [23]; III) absorbance ratio method, which involves formation of Q-absorbance equation at: 1) λ = 265 nm (isobestic point at which both the drugs exhibit absorbance) and $\lambda \text{ max}_{\text{Valsartan}}$ = 249 nm [24]; 2) λ = 258.4 nm (isoabsorptive point) and $\lambda \text{ max}_{\text{Hydrochlorothiazide}}$ = 272.6 nm [25]; IV) area under curve method [24]; V) simultaneous equations method based on the measurement of absorbance at λ = 249.4 nm and λ = 272.6 nm [25].

For simultaneous determination of Valsartan and Amlodipine in tablets have been presented the following methods: 1) first derivative of the ratio spectrum (λ = 290 nm), obtained by ratio of absorption spectrum of mixture of Amlodipine and Valsartan and absorption spectrum of Amlodipine [26]; 2) simultaneous equation method [27]. Valsartan and Ramipril have been analysed by simultaneous equation method using λ = 210 nm and λ = 249 nm and by absorbance correction method [28].

First (D1), second (D2) and third (D3) derivative spectrophotometric methods have been reported for simultaneous determination of Valsartan in combination with statins: Fluvastatin – D1, D2, D3), Pravastatin – D1 and D3, Atorvastatin – D2 and D3 [29].

Different innovative spectrophotometric methods were introduced for simultaneous quantification of Valsartan and Sacubitril in combined dosage form: 1) dual wavelength

method at λ = 226 nm and λ = 275 nm; 2) advanced absorbance subtraction based on iso-absorptive point λiso = 246 nm and λ = 261 nm; 3) ratio difference spectrophotometric method at λ = 225 nm and λ = 264 nm; 4) first derivative of ratio spectra at λ = 232 nm for Valsartan and λ = 239 nm for Sacubitril; 5) mean centering of ratio spectra at λ = 260 nm [30].

For the simultaneous estimation of Valsartan, Amlodipine besylate and Hydrochlorothiazide in combined tablet dosage form have been applied: 1) absorption correction method [31]; 2) formation and solving of simultaneous equations at $\lambda max_{\text{Amlodipine besylate}}$ = 239 nm, $\lambda max_{\text{Valsartan}}$ = 250 nm and $\lambda max_{\text{Hydrochlorothiazide}}$ = 272 nm [32]; 3) first order derivative UV-spectrophotometry [33].

Small differences in the wavelength setting have a great effect on the result for: first, second, third derivative spectrophotometric methods, ratio spectra derivative, first derivative of the ratio spectrum and absorbance ratio method, where errors in the registration of the spectrum are the reason for method non-reproducibility. The advantage of the classical UV-spectrophotometry in comparison with UV-derivative method, is low susceptibility towards changes in the apparatus parameters [34].

Due to these reasons, the aim of current study was the application of the validated UV-spectrophotometric method for determination of Valsartan [35] in pharmaceutical dosage preparations (tablets) in 99.98 % ethanol at λmax = 252 nm and in methanol at λmax = 250 nm.

MATERIALS AND METHODS

I. Drug products: Valsartan 160 mg tabl., produced from Bulgarian pharmaceutical company.
II. Reference standard: Valsartan (98 %) (Sigma Aldrich, N: SML 0142).
III. Reagents with analytical grade of puruty: 99.98 % ethanol (Sigma Aldrich, N: SZBD 0500 V UN 1170), methanol (99.9 %) (Sigma Aldrich, N: SZBD 063AV UN 1230).

METHODS. UV-spectrophotometry.

I. Equippment: UV-VIS diode array spectrophotometer (Hullett Packard N:8452 A).

II. Preparation of test-solution of Valsartan 160 mg tabl. in 99.98 % ethanol and methanol.

From the homogenized tablets of Valsartan 160 mg tabl. (with an average weight) on an analytical balance with an accuracy of 4 characters accurately were weighted 12 samples, containing an amount, equivalent to 160 mg Valsartan. 6 samples were dissolved in 99.98 % ethanol and 6 samples were dissolved in methanol in 100.0 ml volumetric flasks. From the obtained solutions, an aliquot parts of 1.0 ml were diluted separatelly to 100.0 ml with the respective solvent.

III. Preparation of reference solution of Valsartan in 99.98 % ethanol and methanol for quantity analysis of tablets by method of external standard.

An accurately weighted quantity, equivalent to 160 mg of reference standard Valsartan 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 Valsartan with concentration: 8.10^{-6} g/ml. In the same manner was prepared reference solution of Valsartan in methanol with concentration: 8.10^{-6} g/ml.

V. UV-spectrophotometric procedure.

The final test-solutions of Valsartan 160 mg tabl. in 99.98 % ethanol and standard solution of Valsartan in 99.98 % ethanol with a concentration of 8.10^{-6} g/ml were analysed spectrophotometrically at λmax = 252 nm by using as a compensatory solution: 99.98 % ethanol. The absorbances of final test-solutions of tablets in methanol and standard solution of Valsartan in methanol at a concentration of 8.10^{-6} g/ml were mesdured at λmax = 250 nm by using as a blank methanol.

RESULTS AND DISCUSSION

In our previous investigations were estimated specific and molar absorbances for Losartan Potassium and Valsartan [36], UV-spectrophotometric method was applied for Losartan Potassium in tablets [37], and UV-spectrophotometric methods for identification and determination of Telmisartan [38] and Valsartan [35] were validated for analytical parameters: selectivity, linearity, LOD, LOQ [39], accuracy and precision in accordance with International Conference on Harmonization Guidelines [40].

In our previous investigation [35] for validation of the UV-spectrophotometric method for determination of Valsartan in 99.98 % ethanol at λmax = 252 nm and in methanol at λmax = 250 nm, 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 Valsartan, equivalent to: 75 %: 120 mg (V_{120}), 100 %: 160 mg (V_{160}), 125 %: 200 mg (V_{200}) of its concentration in tablets (160 mg). For every mixture were prepared 3 samples by accurately weighed quantity, containing reference standard Valsartan: 120 mg, 160 mg and 200 mg. All samples were dissolved separately in 99.98 % ethanol in volumetric flasks 200.0 ml. Aliquot parts of 1.0 ml of every of 9 resulting solutions were diluted with the same solvent to 100.0 ml. to obtain solutions with concentration of Valsartan respectively: 6.10^{-6} g/ml; 8.10^{-6} g/ml; 1.10^{-5} g/ml. By the same manner were prepared 3 samples from 3 model mixtures of reference standard Valsartan by dissolving in methanol. For linearity, accuracy and precision all solutions in 99.98 % ethanol were analyzed at λmax = 252 nm against blank 99.98 % ethanol and the absorbance of solutions in methanol was measured at λmax = 250 nm, using methanol as blank solution.

Selectivity was proved by the fact that in UV-spectra of blank solutions were not observed the measured absorption at the specific for Valsartan wavelengths. LOD and LOQ are based on regression equations for A < 0.2: y = 88004.x – 9.10-5 (99.98 % ethanol); and y = 53659.x + 0.008 (methanol). For model mixtures accuracy wss represented by the degree of recovery R [%] ± RSD [%] as per ICH Guidelines [40]: Valsartan in ethanol: R C_{V120} : 98.35 % ÷ 103.69 %; R C_{V160} : 97.51 % ÷ 99.11 %; R C_{V200} : 99.5 % ÷ 101.01 %; Valsartan (methanol): R C_{V120}: 95.12 % ÷ 101.44 %; R C_{V160}: 97.74 % ÷ 100.06 %; R C_{V200}: 98.15 % ÷ 100.57 %.

The analytical parameter precision for model mixtures wss characterized by the uncertainty of the result, which is determined by SD, RSD and confidence interval. All results for the obtained quantities of Valsartan suit confidence intervals: in 99.98 % ethanol: C_{V120}: 117.32 mg ÷ 125.34 mg, C_{V160}: 157.06 mg ÷ 157.94 mg, C_{V200}: 199.97 mg ÷ 201.51 mg; in methanol: C_{V120}: 113.51 mg ÷ 122.65 mg; C_{V160}: 157.52 mg ÷ 158.90 mg; C_{V200}: 195.97 mg ÷ 201.89 mg.

In our current study was applied the validated UV-spectrophotometric method for determination of Valsartan [35] in tablets. On Table 1. were presented results for: weighted amounts of Valsartan 160 mg tabl. (average weight: 0.375 g); absorbances of tablet solutions in 99.98 % ethanol at λmax = 252 nm: ($A_{Valsartan\ (E)}$), (Ast = 0.63997) and in methanol at λmax

= 250 nm ($A_{Valsartan\ (M)}$), (Ast = 0.42844); Chauvenet's criterion for absorbances: ($UA_{Valsartan\ (E)}$; $UA_{Valsartan\ (M)}$.

Table 1. Weighted quantities of Valsartan 160 mg tabl. and absornances.

	99.98 % Ethanol			Methanol		
N :	Weighted $_{Valsartan\ (E)}$	$A_{Valsartan\ (E)}$	U $A_{Valsartan\ (E)}$	Weighted $A_{Valsartan\ (M)}$	$A_{Valsartan\ (M)}$	U $A_{Valsartan\ (M)}$
1.	0.3464	0.59158	1.19	0.3721	0.42160	1.27
2.	0.3570	0.60838	0.63	0.3725	0.42215	0.14
3.	0.36	0.61359	0.46	0.3738	0.42580	0.22
4.	0.3772	0.64493	0.59	0.3750	0.42832	0.41
5.	0.3798	0.64949	0.74	0.3762	0.43050	0.95
6.	0.3846	0.65584	0.95	0.3765	0.43176	1.27
$\overline{X}$ ± SD		0.6273 ± 0.03			0.42669 ± 0.004	
SD		0.03			0.004	
RSD [%]		4.78			0.94	

On Table 2., were summarized results for: obtained content by method of external standard of Valsartan in tablets: $C_{Val\ (E)}$, $C_{Val\ (M)}$, after application of spectrophotometric method, degree of recovery [%]: R $C_{Val\ (E)}$, R $C_{Val\ (M)}$; Chauvenet's criterion for obtained content of Valsartan: $UA_{Valtensin\ (E)}$; $UA_{Valtensin\ (M)}$, for N – number of individual measurements (1 ÷ 6); $\overline{X}$ – mean arithmetic error; S $\overline{X}$ – mean square error; E [%] – relative error; P – confidence possibility [%], t – coefficient of Student.

Table 2. Obtained content of Valsartan 160 mg tabl.

	99.98 % Ethanol			Methanol		
N:	$C_{Val\ (E)}$ [mg]	R $C_{Val\ (E)}$ [%]	U $C_{Val\ (Et)}$	$C_{Val\ (M)}$ [mg]	R $C_{Val\ (M)}$ [%]	U $C_{Val(Met)}$
1.	160.11	100.07	0.32	158.67	99.17	1.19
2.	159.77	99.86	1.04	158.71	99.19	1.14
3.	159.80	99.88	0.92	159.52	99.7	0.13
4.	160.30	100.19	1.08	159.96	99.98	0.43
5.	160.33	100.21	1.20	160.26	100.16	0.8
6.	159.87	99.92	0.64	160.6	100.38	1.23

$\overline{X}$ ± SD	160.03 ± 0.25			159. 62 ± 0.8		
$\bar{R}$ [%] ± RSD [%]		100.02 ± 0.16			99.76 ± 0.5	
SD	0.25	0.16		0.8	0.5	
RSD [%]	0.16	0.16		0.5	0.5	
S $\overline{X}$	0.1	0.07		0.33	0.2	
P [%]	98.0	98.0		98.0	98.0	
T	3.37	3.37		3.37	3.37	
t.S $\overline{X}$	0.34	0.24		1.11	0.67	
$\overline{X}$ ± t.S $\overline{X}$	159.69÷ 160.37	99.78÷ 100.26		158.51 ÷ 160.73	99.09 ÷ 100.43	
E [%]	0.06	0.07		0.21	0.2	

Data for Chauvenet's criteria for absobances and for obtained by method of external standard content of Valsartan are lower than maximum permissible value (U = 1.73; N = 6), which is applied for the assessment of the need for the removal of sharply different results. The analytical parameter repeatability for tablets is characterized by the uncertainty of the result, which includes standard deviation (SD), relative standard deviation (RSD) and confidential interval ($\overline{X}$ ± t.S $\overline{X}$ = $\overline{X}$) [40]. Relative error is lower than 0.25 %.

Conclusion.

The validated external standard UV-spectrophotometric was applied. for determination of Valsartan in pharmaceutiocal dosage preparations (tablets) in 99.98 % ethanol at λmax = 252 nm and in methanol at λmax = 250 nm. All of the experimental data correspond to the respective confidence intervals at the confidence probability. 98 %: in 99.98 % ethanol: 159.69 mg ÷ 160.37 mg; in methanol: 158.51 mg ÷ 160.73 mg. The validated method can be applied for the determination of Valsartan in dosage drug preparations.

Conflicts of interests.
All authors have none to declare.

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