Original Article

Estimation of validation parameters of UV-Spectrophotometric method for analysis of Valsartan

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ABSTRACT

The aim of recent investigation was the estimation of the validation analytical parameters selectivity, linearity, LOD, LOQ, accuracy and precision for UV-spectrophotometric method for analysis of Valsartan at λmax = 252 nm (99.98 % ethanol) and λmax = 250 nm (methanol). Selectivity was proved by the fact that in UV-spectra of blank solution was not observed the measured absobance at Valsartan specific wavelengths. The experimental results were subjected to a linear regression analysis: 99.98 % ethanol: y = 81628.x – 0.0226 (A > 0.2); y = 88004.x – 9.10^{-5} (A < 0.2); methanol: 39508.x + 0.095 (A > 0.2); 53659.x + 0.008 (A < 0.2). Linearity is characterized by coefficient of linear regression: $R^2 > 0.98$. In 99.98 % ethanol LOD = $1.84.10^{-9}$ g/ml; LOQ = $6.12.10^{-9}$ g/ml; in methanol: LOD = $9.4.10^{-8}$ g/ml; LOQ = $3.16.10^{-7}$ g/ml. Accuracy is represented by the degree of recovery, which suit confidence intervals:

1) 99.98 % ethanol: RC_{V160} : 97.51 % ÷ 99.11 %; 2) methanol: RC_{V160}: 97.74 % ÷ 100.06 %.
Results for precision correspond to the relevant interval:

1) 99.98 % ethanol: C_{V160}: 157.06 mg ÷ 157.94 mg; 2) methanol: C_{V160}: 157.52 mg ÷ 158.90 mg.

Keywords: Valsartan, UV-spectrophotometry, validation, accuracy, precision, linearity.

Introduction

Angiotensin-receptor antagonists Irbesartan [1-8], Olmesartan [2,9-12] and Valsartan (Figure 1) [3,13-19] are applied for theatment of high blood pressure.

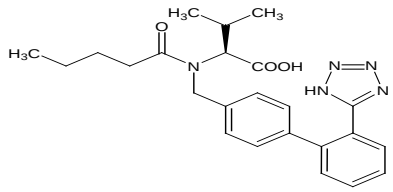

Figure 1: Chemical structure of Valsartan.

For analysis of sartans often are applied UV-spectrophotometry [4,20-24] and HPLC [2,25-30]. For determination of Valsartan in pure form are described HPLC (λ = 233 nm) [5,31-36] and UV-spectrophotometry [6,37-50] and for tablets are reported: HPLC: λ = 210 nm [7]; λ = 273 nm [8,51-66]; λ = 265 nm and second derivative UV-spectrophotometry. [9,67-71] First-derivative UV-spectrophotometry and HPLC were used for simultaneously determination of Valsartan and Hydrochlorothiazide in dosage forms. [10,72-77]

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HPLC disadvantage is the requirement of a skilled technician for monitoring. The disadvantage of derivative spectrophotometry is susceptibility towards changes in the apparatus parameters. Small differences in the wavelength setting have a great effect on the result, especially in the zero-crossing technique, 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 HPLC is that is inexpensive and easy to use. In comparison with UV-derivative method, conventional UV-method is with low susceptibility towards changes in the apparatus parameters. [11,78-85]

Due to these reasons, the aim of current study was the estimation of the validation analytical parameters selectivity, linearity, LOD, LOQ, accuracy and precision for conventional UV-spectrophotometric method for analysis of Valsartan in 99.98 % ethanol at λmax = 252 nm and in methanol at λmax = 250 nm.

Materials

I. Reference standard: Valsartan (98 %) (Sigma Aldrich, N: SML 0142).
II. 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. Validation of analytical parameter linearity.

1. Preparation of solutions of reference standard Valsartan in 99.98 % ethanol and methanol.

An accurately weighed quantities from reference standard Valsartan were dissolved in a volumetric flask of 200.0 ml respectively in 99.98 % ethanol (10 mg, 20 mg, 60 mg, 120 mg, 140 mg, 160 mg, 200 mg) and methanol (24 mg, 34 mg, 50 mg, 70 mg, 120 mg, 160 mg, 200 mg). From every

solution an aliquot part of 1.0 ml separately was diluted with 99.98 % ethanol to 100.0 ml (5.10^{-7} g/ml; 1.10^{-6} g/ml; 3.10^{-6} g/ml; 6.10^{-6} g/ml; 7.10^{-6} g/ml; 8.10^{-6} g/ml; 1.10^{-5} g/ml) and in methanol ($1.2.10^{-6}$ g/ml; $1.7.10^{-6}$ g/ml; $2.5.10^{-6}$ g/ml; $3.5.10^{-6}$ g/ml; 6.10^{-6} g/ml; 8.10^{-6} g/ml; 1.10^{-5} g/ml).

2. Preparation of model mixtures of reference standard Valsartan 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 Valsartan, equivalent to: 75 %: 120 mg (V120), 100 %: 160 mg (V160), 125 %: 200 mg (V200) 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 λ = 252 nm against blank 99.98 % ethanol and the absorbance of solutions in methanol was measured at λ = 250 nm, using methanol as blank solution.

3. Root limit mean square error method (RMSE) for the determination of limit of detection (LOD) and limit of quantitation (LOQ).

Calibration curves were constructed by analysis of solutions with low concentrations (absorbance A < 0.2). The data were subjected to linear regression analysis and the linear correlation coefficients (R^2) were obtained. From the regression equation: y = a.x + b were calculated the predictable absorbance value (Ap); the error E = |Ap - A|; E2 = [|Ap - A |]^2, $E1=\frac{\sum E2}{n-2}$; RMSE = $\sqrt{E1}$; LOD = 3.RMSE/a; LOQ = 10.RMSE/a. [12]

Results and Discussion.

I. Validation of UV-spectrophotometric method. [13-15]

1) Selectivity.

In the same manner like solutions with reference standard Valsartan, blank solutions respectively in 99.98 % ethanol and in methanol were prepared for the estimatiton of analytical parameter selectivity. In blank solutions was included the used in tablets supplement starch without the active ingredient Valsartan.

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.

Spectra for linearity and precision for Valsartan reference standard in 99.98 % ethanol and methanol are illustrated on Fig. 2., Fig. 3. and Fig.4.

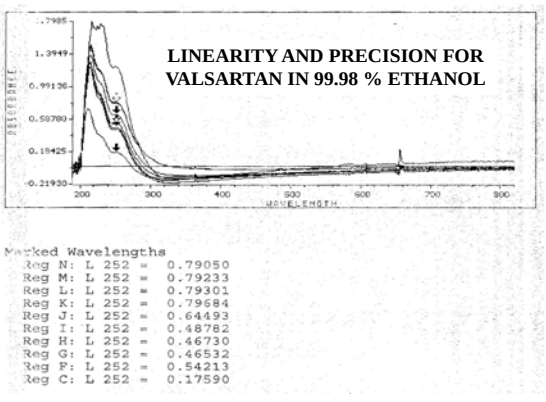


Figure 2: Linearity and precision for Valsartan reference standard in 99.98 % ethanol.

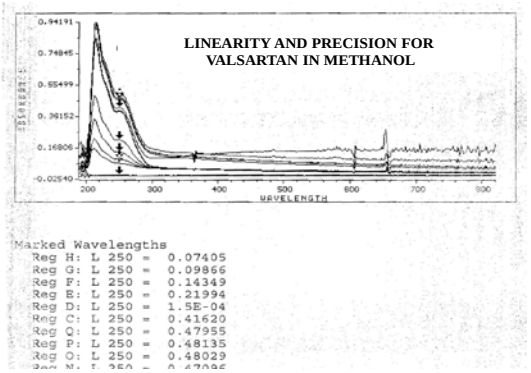


Figure 3: Linearity and precision for Valsartan reference standard in methanol.

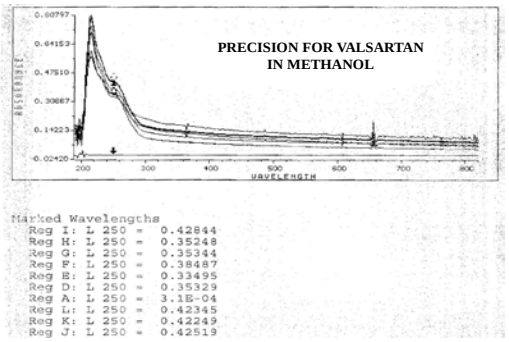


Figure 4. Precision for Valsartan reference standard in methanol.

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

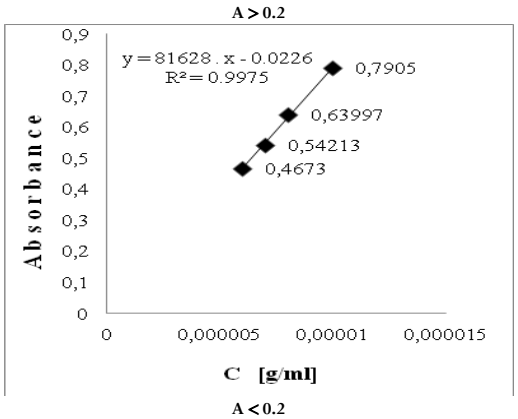
Linearity is the range within the signal from the detector remains in linear dependency from the concentration of analyte. [13-15]

From standard Valsartan were prepared a series of solutions with increasing concentrations. For A > 0.2 and A < 0.2 for every concentration the values of the absorbance (A) at the respective wavelenght were measured and resuts are summarized on Table 1.

Table 1. Concentrations and absorbanses for referense standard Valsartan in 99.98 % ethanol and methanol.

	99.98 % Ethanol		Methanol	
	Concentration [g/ml]	Absorbanse (AU)	Concentration [g/ml]	Absorbanse (AU)
1	5.10^{-7}	0.04388	$1.2.10^{-6}$	0.07405
2	1.10^{-6}	0.08795	$1.7.10^{-6}$	0.09866
3	3.10^{-6}	0.17590	$2.5.10^{-6}$	0.14349
4	6.10^{-6}	0.46730	$3.5.10^{-6}$	0.21994
5	7.10^{-6}	0.54213	6.10^{-6}	0.35248
6	8.10^{-6}	0.63997	8.10^{-6}	0.41620
7	1.10^{-5}	0.79050	1.10^{-5}	0.47955
7	1.10^{-5}	0.79050	1.10^{-5}	0.47955

Results were subjected to a linear regression analysis. Linearity at A > 2 and A < 0.2 is illustrated by the calibration curves: Fig 5. (99.98 % ethanol) and Fig 6. (methanol).



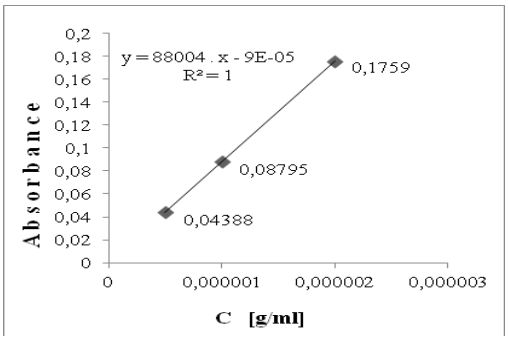


Figure 5. Linearity for Valisartan in 99.98 % ethanol (λ = 252 nm).

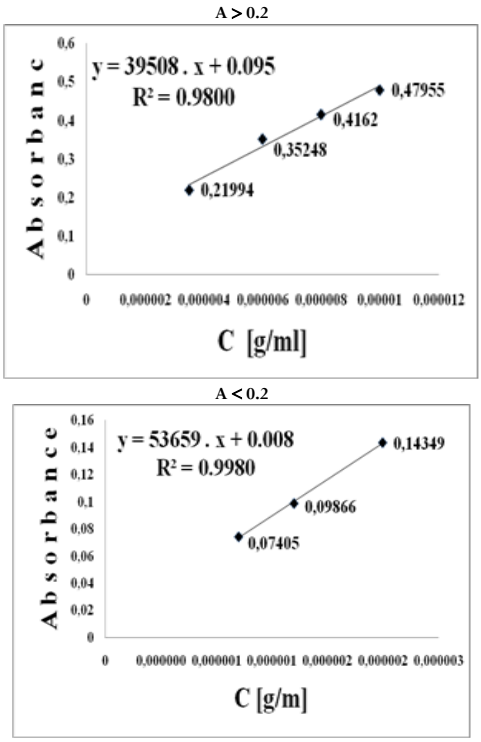


Figure 6. Linearity for Valisartan in methanol (λ = 250 nm).

On Table 2. are included parameters of regression equations for Valsartan for A > 0.2 and A < 0.2, where: λ max [nm] – absorbance maximum. Linearity is characterized by coefficient of linear regression, which is $R^2 > 0.98$.

Table 2. Characteristics of the UV-method by parameters of regression equations.

N:	Parameters	99.98 % Ethanol		Methanol	
		A > 0.2	A < 0.2	A > 0.2	A < 0.2
1.	λ max (nm)	252	252	250	250
2	Concentration range (g/ml)	6.10^{-6} ÷1.10^{-5}	5.10^{-7} ÷3.10^{-6}	$3.5.10^{-6}$ ÷ 1.10^{-5}	$1.2.10^{-6}$ ÷ $2.5.10^{-6}$
3.	Regression equation	81628.x – 0.0226	88004.x -9.10^{-5}	39508.x + 0.095	53659.x +0.008
4.	Slope (a)	81628	88004	39508	53659
5.	Intersept (b)	– 0.0226	-9.10^{-5}	0.095	0.008
6.	Correlation coefficient (R^2)	0.9975	1	0.9800	0.9980

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

LOD and LOQ are based on regression equations for A < 0.2: y = 88004.x – 9.10^{-5} (99.98 % ethanol) (Table 3.) and y = 53659.x + 0.008 (methanol) (Table 4.) by application of RMSE-method.

Table 3. RMSE-method for LOD and LOQ for Valsartan in 99.98 % ethanol.

C [g/ml]	A	Ap	| A – Ap|	$E^2 = [\|A_p - A\|]^2$	E1=	RMSE= $\sqrt{E1}$
					$\frac{\sum E2}{n-2}$	
2.10^{-6}	0.17590	0.17592	0.00002	4.10^{-10}		
1.10^{-6}	0.08795	0.08791	0.00004	$1.6.10^{-9}$	$2.9.10^{-9}$	$5.39.10^{-5}$
5.10^{-7}	0.04388	0.04391	0.00003	9.10^{-10}		
Linear range [g/ml]				5.10^{-7} ÷ 3.10^{-6}		
LOD [g/ml]				$1.84.10^{-9}$		
LOQ [g/ml]				$6.12.10^{-9}$		

Table 4. RMSE-method for LOD and LOQ for Valsartan in methanol.

C [g/ml]	A	Ap	| A – Ap|	$E^2 = [\|A_p - A\|]^2$	E1= $\frac{\sum E2}{n-2}$	RMSE = $\sqrt{E1}$
$2.5.10^{-6}$	0.14349	0.14295	0.00054	$2.91.10^{-7}$		
$1.7.10^{-6}$	0.09866	0.10002	0.00136	$1.85.10^{-6}$	$2.88.10^{-6}$	$1.7.10^{-3}$
$1.2.10^{-6}$	0.07405	0.07319	0.00086	$7.39.10^{-7}$		
Linear range [g/ml]				$1.2.10^{-6}$ ÷ $2.5.10^{-6}$		
LOD [g/ml]				$9.4.10^{-8}$		
LOD [g/ml]				$3.16.10^{-7}$		

4. Accuracy

Accuracy is the degree of correspondence between the obtained average result of repeated analysis and the actual value. [13-15] On Table 5. are presented data for added content of standard Valsartan in 3 samples for 3 model mixtures in 99.98 % ethanol and methanol: V120 (120 mg, 75 %); (average weight (AV) = 0.28 g); V160 (160 mg, 100 %) (AV) = 0.38 g); V200 (200 mg, 125 %) (AV) = 0.47 g).

Table 5. Added content of reference standard Valsartan in model mixtures.

N:	Added V120 [mg]	Weighed V120 [g]	Added V160 [mg]	Weighed V160 [g]	Added V200 [mg]	Weighed V200 [g]
			99.98 % ethanol			
1.	119.4	0.2786	159.6	0.3791	199.5	0.4688
2.	120.1	0.2802	160.2	0.3805	200.3	0.4707
3.	120.8	0.2819	160.8	0.3819	200.7	0.4716
			Methanol			
1.	119.49	0.2788	159.07	0.3778	199.79	0.4695
2.	120.3	0.2807	160.42	0.3810	200.21	0.4705
3.	120.6	0.2814	160.51	0.3812	200.68	0.4716

On Table 6. are included the results for absorbances in 99.98 % ethanol: A_{V120} (Ast = 0.46730); A_{V160} (Ast = 0.63997); A_{V200} (Ast = 0.79050) and methanol: A_{V120} (Ast = 0.35248); A_{V160} (Ast = 0.42844); A_{V200} (A st = 0.47955) and Chauvenet's criterion for absorbances: U.

Table 6. Absorbances for model mixtures with reference standard Valsartan at λ = 252 nm (99.98 % ethanol) and λ = 250 nm (methanol).

N :	A_{V120}	U A_{V120}	A_{V160}	U A_{V160}	A_{V200}	U A_{V200}
			99.98 % ethanol			
1.	0.46532	0.76	0.62982	0.95	0.79301	0.53
2.	0.46555	0.74	0.63016	0.61	0.79233	0.87
3.	0.48782	1.49	0.63234	1.57	0. 79684	1.39
$\bar{X}$	0.47290		0.63077		0.79406	
SD	0.01		0.001		0.002	
RSD[%]	2.11		0.16		0.25	
			Methanol			
	A_{V120}	U A_{V120}	A_{V160}	U A_{V160}	A_{V200}	U A_{V200}
1.	0.33495	1.23	0.42249	1.22	0.47096	0.66
2.	0.35329	0.61	0.42345	0.26	0.48029	0.28
3.	0.35344	0.62	0.42519	1.48	0. 48135	0.38
$\bar{X}$	0.34723		0.42371		0.47753	
SD	0.01		0.001		0.01	
RSD [%]	2.88		0.24		2.09	

Results for the estimation of accuracy for mixtures with Valsartan are presented on Table 7. (99.98 % ethanol) and Table 8. (methanol), where: C – obtained content of Valsartan by method of external standard; R – degree of recovery [%]; U – Chauvenet's criterion for the quantities of Valsartan; N – number of individual measurements (1 ÷ 3); – mean arithmetic error; S – mean square error; E (%) – relative error; P – confidence possibility: 95 %, t – coefficient of Student: 2.57.

Table 7. Content of Valsartan in model mixtures in 99.98 % ethanol.

N:	C_{V120} [mg]	R C_{V120} [%]	U C_{V120}	C_{V160} [mg]	R C_{V160} [%]	U C_{V160}	C_{V200} [mg]	R C_{V200} [%]	U C_{V200}
1.	120.09	100.58	0.46	157.84	98.9	1.13	201.15	100.83	0.79
2.	119.47	99.48	0.69	157.34	98.21	0.53	200.16	99.93	1.12
3.	124.43	103.0	1.15	157.31	97.83	0.63	200.92	100.11	0.35
$\overline{X}$ ± SD	121.33 ± 2.7			157.5 ± 0.3			200.74 ± 0.52		
$\overline{R}$ [%]± RSD[%]		101.0 ± 1.78			98.31 ±0.55			100.29 ± 0.48	
SD	2.7	1.8		0.3	0.54		0.52	0.48	
RSD [%]	2.23	1.78		0.19	0.55		0.26	0.48	
S $\overline{X}$	1.56	1.04		0.17	0.31		0.3	0.28	
P [%]	95.0	95.0		95.0	95.0		95.0	95.0	
t	2.57	2.57		2.57	2.57		2.57	2.57	
t. S $\overline{X}$	4.01	2.67		0.44	0.8		0.77	0.72	
$\overline{X}$ –t.S $\overline{X}$ ÷ $\overline{X}$ +t.S $\overline{X}$	117.32 ÷ 125.34	98.35 ÷ 103.69		157.06 ÷ 157.94	97.51 ÷ 99.11		199.97 ÷ 201.51	99.5 ÷ 101.01	
E [%]		1.03		0.11	0.32		0.15	0.28	

Table 8. Content of Valsartan in model mixtures in methanol.

N:	C_{V120} [mg]	R C_{V120} [%]	U C_{V120}	C_{V160} [mg]	R C_{V160} [%]	U C_{V160}	C_{V200} [mg]	R C_{V200} [%]	U C_{V200}
1.	114.52	95.84	1.16	158.7	99.77	0.94	196.63	98.42	1.16
2.	119.98	99.73	0.62	157.72	98.32	1.06	200.1	99.95	0.59
3.	119.73	99.28	0.54	158.29	98.62	0.1	200.07	99.7	0.57
$\overline{X}$ ± SD	118.08 ± 3.08			158.24 ± 0.49			198.93 ± 1.99		
$\overline{R}$ [%]± RSD[%]		98.28 ±2.17			98.9 ±0.78			99.36 ±0.83	
SD	3.08	2.13		0.49	0.77		1.99	0.82	
RSD [%]	2.61	2.17		0.31	0.78		1.0	0.83	
S $\overline{X}$	1.78	1.23		0.28	0.45		1.15	0.47	
P [%]	95.0	95.0		95.0	95.0		95.0	95.0	
t	2.57	2.57		2.57	2.57		2.57	2.57	
t. S $\overline{X}$	4.57	3.16		0.72	1.16		2.96	1.21	
$\overline{X}$ –t.S $\overline{X}$ ÷ $\overline{X}$ +t.S $\overline{X}$	113.51 ÷ 122.65	95.12 ÷ 101.44		157.52 ÷ 158.90	97.74 ÷ 100.06		195.97 ÷ 201.89	98.15 ÷ 100.57	
E [%]	1.51	1.25		0.18	0.46		0.58	0.47	

Accuracy is represented by the degree of recovery R [%] ± RSD [%} as per ICH guidelines. [13-15] Results show that at the used confidence possibility all data for R suit respective interval.

Data for Chauvenet's criterion are lower than maximum permissible value (U = 1.68; N = 3), which is applied for the assessment of the need for the removal of sharply different results.

5) Precision (repeatability)

Repeatability is characterized by the uncertainty of the result, which includes standard deviation (SD), relative standard deviation (RSD) and confidential interval ($\overline{X} \pm t.S\,\overline{X}$).[13-16,86-91] At the corresponding confidence possibility, all results for the obtained quantities of Valsartan suit the appropriate confidence interval.

Conclusion

UV-spectrophotometric method for determination of Valsartan in 99.98 % ethanol and in methanol by method of external standard was validated for analytical parameters: selectivity, linearity, LOD, LOQ, accuracy and precision. Results fot accuracy and repeatability suit respective confidence intervals. 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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