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Research Article

Novel HPLC-UV method for simultaneous determination of valsartan and atenolol in fixed dosage form; Study of green profile assessment

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Abstract

Aim of this work was to develop the first simple, rapid, green, economical and selective HPLC method for simultaneous quantification of the cited drugs in their challenging binary mixture. The work was motivated by the global trends towards sustainable chemistry in designing eco-friendly mobile system without affecting the analysis parameters. The proposed method was subjected to a greenness profiles using some metrics as Eco-scale.

Materials and methods. This was accomplished under the following chromatographic conditions: HPLC column Discovery C18 (4.6 mm i.d. × 150 mm, 5 µm), column temperature 30 °C, flow rate 1.0 mL/min, mobile phase composed of 20% acetonitrile, 80% of 0.16% ammonium acetate and 0.2% of 1.5 M tetramethylammonium hydroxide (V/V) and signal monitoring at a wavelength of 225 nm and 237 nm.

Results. A conventional mixture of acetonitrile and 0.16% ammonium acetate was tried in different ratios, but the drugs were not well separated. The shortest aliphatic chain cationic ion pair reagent tetramethylammonium hydroxide should not be exchanged with other type similar with this, like tetramethylammonium hydrogen sulfate, it did not work to our experiments. Increasing salt concentration, ammonium acetate, more than 0.2%, pushes the peak of atenolol closer to dead volume, which is negative. Atenolol in their methods for multicomponent mixtures elutes in dead volume, or when retained longer, much stronger, hydrophobic mobile phase should be used if valsartan should be seen in same chromatogram at dissent time. The 237 nm can be chosen as compromise signal for nearly equal peaks height with high sensitivity is not essential. The 225 nm signal shows much higher sensitivity for atenolol and less increase for valsartan peaks, which can be used when higher sensitivities will be essential. Linearity was examined and proven at different concentration levels in the range of working concentration of valsartan (0.16–0.96 mg/mL) and atenolol (0.2–1.20 mg/mL). The high value of recoveries obtained for valsartan and atenolol indicates that the proposed method was found to be accurate. The results of proposed method found to be an excellent green analysis with a score of 84.

Conclusion. A new fast, simple and green, but selective, accurate, precise and robust HPLC-UV method for simultaneous determination of valsartan and atenolol in newly formulated dosage form was developed and many possible variations of the same were suggested. The developed method for the simultaneous quantification of valsartan and atenolol in their challenging binary mixture offers simplicity essential for quality control of a large number of samples in short time intervals, which is necessary for routine analysis. The method was subjected to greenness profile assessment.

Keywords

Valsartan, Atenolol, HPLC-UV, Method Development, Validation, Green chemistry

Introduction

Green chemistry is at the frontiers of this continuously-evolving interdisciplinary science and publishes research that attempts to reduce the environmental impact of the chemical enterprise by developing a technology base that is inherently non-toxic to living things and the environment. High performance liquid chromatography (HPLC) is one of the most common and versatile technique in the pharmaceutical analysis field. It provides an automated, simple, fast and cost-efficient technique for separation, identification and quantification of complex mixtures with high resolution and reproducibility. Moreover, HPLC has taken significant steps towards green analytical chemistry. This is fulfilled by simultaneous analysis of multiple samples with the lowest energy and mobile phase consumption or wastes per sample in the realm of liquid chromatography.

The urgency of the problem of hypertension is determined by its high population frequency, impact on health status, performance and life expectancy of the population. World and national guidelines for the diagnosis and treatment of hypertension emphasize that virtually all groups of drugs for the treatment of hy pertension can be combined with each other, of course, that the recent trend of combining different pharmacological subgroups to achieve a more effective therapeutic effect. Therefore, the creation of fixed combinations of API (active pharmaceutical ingredients) antihypertensive action in the form of solid dosage forms is a task of modern pharmacy.

Valsartan (Fig. 1) is chemically described as (2*S*)-3-methyl-2-[pentanoyl-[[4-[2-(2*H*-tetrazol-5-yl)phenyl] phenyl]methyl]amino]butanoic acid. Valsartan is an orally active nonpeptide triazole-derived antagonist of angiotensin (AT) II with antihypertensive properties. Valsartan selectively and competitively blocks the binding of angiotensin II to the AT1 subtype receptor in vascular smooth muscle and the adrenal gland, preventing AT II-mediated vasoconstriction, aldosterone synthesis and secretion, and renal reabsorption of sodium, and resulting in vasodilation, increased excretion of sodium and water, a reduction in plasma volume, and a reduction in blood pressure. Therefore, analytical methods for their separation and quantification in pharmaceutical formulations and inhuman plasma are desirable for quality control and therapeutic drug monitoring, respectively. Several techniques have been reported in the literature for the determination of valsartan individually in pharmaceutical dosage forms or human serum samples such as spectrophotometry (Gupta et al. 2010) high performance liquid chromatography-tandem mass spectrometry (LC–MS/MS) (Shah et al. 2009; Gonzaleza et al. 2010), HPLC methods with photometric (Raju and Rao 2011), fluorometric detection coupled with mass spectrometry (Rao et al. 2011) and high performance capillary electrophoresis (HPCE) (Hillaert and Bossche 2002, 2003; Alnajjar 2011) as well as the derivative UV-spectrophotometry methods (Tatar and Saglik 2002; Kul et al. 2010).

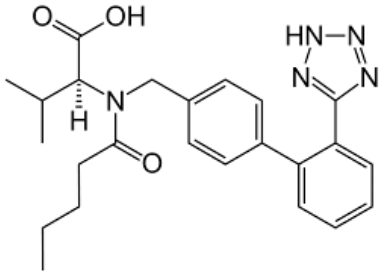

Figure 1. Chemical structure of valsartan.

Atenolol (Fig. 2) is a synthetic isopropylamino-propanol derivative used as an antihypertensive, hypotensive and antiarrhythmic. Atenolol is chemically known as 2- [4 – [(2RS) -2-hydroxy-3 – [(1-methylethyl) amino] propoxy] phenyl] acetamide. Atenolol acts as a peripheral, cardioselective beta-blocker specific for beta-1 adrenergic receptors, without intrinsic sympathomimetic effects. It reduces exercise heart rates and delays atrioventricular conduction, with overall oxygen requirements decreasing. Literature survey reveals that various analytical methods have been reported for determination of Atenolol in pure form and in pharmaceutical formulations which include high performance liquid chromatography (HPLC) for determination of Atenolol in tablets (Kondratova et al. 2016; Logoyda 2018a, b, c, d; Logoyda et al. 2018a, b; Logoyda 2019a, b).

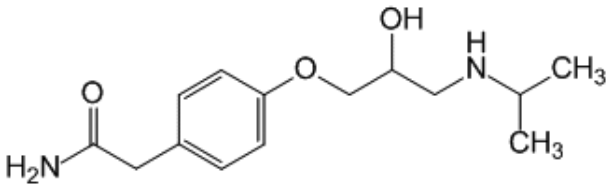

Figure 2. Chemical structure of atenolol.

This unique combination is safe and effective for treating hypertension in elderly people than using each drug alone. But to date, no chromatographic method has been reported for the assaying of this binary mixture.

Aim of work

Therefore, the aim of this work was to develop the first simple, rapid, green, economical and selective HPLC method for simultaneous quantification of the cited drugs in their challenging binary mixture. The work was motivated by the global trends towards sustainable chemistry in designing eco-friendly mobile system without affecting the analysis parameters. The proposed method was subjected to a greenness profiles using some metrics as Eco-scale.

Materials and methods

Valsartan (purity 99.9%) was purchased from Tonira PHARMA LIMITED (Gujarat – India), atenolol (purity 100.1%) was purchased from Moehs Catalana (Barcelona – Spain). 80 mg valsartan (standard sample) and 100 mg atenolol (standard sample) were put in 100 mL measuring flasks and dissolved in 50 mL 50% v/v methanol, ultrasound crushed and treated for 2 minutes and shaked 15 min with orbital shaker. The final concentrations were 1 mg/mL for atenolol and 0.8 mg/mL for valsartan. Samples were filtered with RC 0.45 μm syringe filters and injected.

Methanol and acetonitrile used in experiments was HPLC gradient grade and ammonium acetate and tetramethylammonium hydroxide were of Ph. Eur. reagent grade and purchased from Merck Darmstdat, Germany. Analytical Balance Mettler Toledo MPC227, pH-meter Metrohm 827, deionized water from TKA Micro system, with final conductivity less than 0.05 μS/cm. IKA orbital shaker KS4000i was used for sample agitation. The nylon and regenerated cellulose RC 0.45 μm syringe filters were purchased from Agilent Technologies.

Dionex Ultimate 3000 UHPLC system controlled by Chromeleon version 6,80, composed of quaternary LPG pump ultimate 3000, autosampler ultimate 3000, ultimate 3000 column compartment, four channel UV-Vis detector ultimate 3000 RS. Shimadzu Nexera XR UPLC system with LPG Quaternary Pump LC-20AD with degasser DGU-20A5R, Autosampler SIL-20AC, PDA detector M20-A, Column Oven and Controller CBM-20A controlled by Lab Solutions version 5,97. The used column Discovery C18 (4.6 mm i.d. × 150 mm, 5 μm), purchased from Sigma-Aldrich Supelco.

Chromatographic conditions:

The optimum mobile phase composition was composed of 20% acetonitrile, 80% of 0.16% ammonium acetate and 0.2% of 1.5 M tetramethylammonium hydroxide (V/V), pumped with 1.0 mL/min at 30 °C set temperature of column oven, with UV detector set to 225 nm and 237 nm wavelength. Analysis performed on column Discovery C18 (4.6 mm i.d. × 150 mm, 5 μm).

Sample preparation

Twelve tablets of each preparation were studied to obtain statistically significant results. The tablets with declared contents of 80 mg valsartan and 100 mg of atenolol were purchased from local drug store, pharmacy. The tablets were put in 100 mL measuring flasks and dissolved in 50 mL 50% v/v methanol, ultrasound crushed and treated for 2 minutes and shaked 15min with orbital shaker. After that measuring flasks were filled to mark for 100 mL, the final concentrations were 1mg/mL for atenolol and 0.8 mg/mL for valsartan. Samples were filtered with RC 0.45 μm syringe filters and injected.

Results and discussion

The emerging of new pharmaceutical formulations provokes the necessity for simple, accurate, economical and fast analytical techniques to be applied in quality control laboratories where time and cost are critical. Moreover, minimizing toxicity with retaining method efficacy may be one of challenging aspects in developing a safer methodology. To find the appropriate HPLC conditions for separation of the examined drug, various columns, isocratic and gradient mobile phase systems were tried, and successfully attempts were performed using a C18 chromatographic column Discovery C18 (4.6 mm i.d. × 150 mm, 5 μm). Method development was initiated by trying several mobile phases with various compositions to attain optimum separation and resolution (Kondratova et al. 2016; Logoyda 2018a, b, c, d; Logoyda et al. 2018a, b; Logoyda 2019a, b). First, a conventional mixture of acetonitrile and 0.16% ammonium acetate was tried in different ratios, but the drugs were not well separated. The shortest aliphatic chain cationic ion pair reagent tetramethylammonium hydroxide was purchased from Sigma, as 1.5 M or ~25% w/v solution and should not be exchanged with other type similar with this, like tetramethylammonium hydrogen sulfate, it did not work to our experiments. Increasing salt concentration, ammonium acetate, more than 0.2%, pushes the peak of atenolol closer to dead volume, which is negative. We consulted more some articles for atenolol retention examination with other very hydrophobic and much less polar component and concluded that they are unusable. Atenolol in their methods for multicomponent mixtures elutes in dead volume, or when retained longer, much stronger, hydrophobic mobile phase should be used if valsartan should be seen in same chromatogram at dissent time. With 1mg/mL solution of atenolol and 0.8 mg/mL solution of valsartan, visibly more sensitive 225 nm signal might create worse linearity, CV below 0.999, but the signal at 237 nm creates perfect CV=1. So, if needed to work at 225 nm, solutions would like to dilute the samples to final concentration of atenolol 0.5 mg/mL and valsartan to 0.4 mg/mL. This step is not essential but shows slightly better CV of linear response. The applicability of the mo-

bile phase concept was tested on chromatographic systems and columns with different performances, and the obtained chromatograms are shown in Figs 3, 4.

The 237 nm can be chosen as compromise signal for nearly equal peaks height with high sensitivity is not essential. The 225 nm signal shows much higher sensitivity for atenolol and less increase for valsartan peaks, which can be used when higher sensitivities will be essential. Chromatograms were obtained with satisfactory retention factors and very good peak symmetry of both analyte peaks (tailing factors according to USP of around 1.2–1.4), with resolution better than required (R > 7) (Logoyda 2019). This was accomplished under the following chromatographic conditions: HPLC column Discovery C18 (4.6 mm i.d. × 150 mm, 5 µm), column temperature 30 °C, flow rate 1.0 mL/min, mobile phase composed of 20% acetonitrile, 80% of 0.16% ammonium acetate and 0.2% of 1.5 M tetramethylammonium hydroxide (V/V) and signal monitoring at a wavelength of 225 nm and 237 nm. The method was validated according to the ICH guideline for the Validation of analytical procedures Q2(Q1A (R2) 2003; Q2A 1994; Q2B 1996).

Specificity

The specificity of the method was determined with evaluation of the obtained chromatograms of the blank, placebo solution, test solution and standard solution. For comparison was added chromatogram of solvent, which should be almost identical to placebo, which confirms selectivity of the method. The chromatograms showed that there is no interference between the principal peaks of bisoprolol and enalapril with the components of placebo and the used solvent, and also good resolution (Fig. 4).

Linearity

Calibration curve representing the relation between the concentrations of drugs versus the peak area were constructed. In triplicate run from which the linear regression equation was calculated. Chromatogram obtained under linearity study in 6 concentrations levels is presented in Figs 5, 6. Linearity was examined and proven at different concentration levels in the range of working concentration of valsartan (0.16–0.96 mg/mL) and atenolol (0.2–1.20 mg/mL). The calibration plots of valsartan and atenolol are presented in Figs 7, 8.

For valsartan, linearity regression equation at 225 nm y = 2E+06x-43093 and an obtained correlation coefficient of R^2 = 1, linearity regression equation at 237 nm y = 2E+06x-10485 and an obtained correlation coefficient of R^2 = 1. For atenolol, linearity regression equation at 225 nm y = 2E+06x+86277 and an obtained correlation coefficient of R^2 = 0.9994, linearity regression equation at 225 nm y = 522282x+ 7976.6 and an obtained correlation coefficient of R^2 = 1. At 225 nm, the values of LOD were 0.15 mg/mL, LOQ were 0.8 mg/mL for atenolol, and LOD were 0.2 mg/mL and LOQ were 0.9 mg/mL for valsartan. The results show that a phenomenal relationship between peak area and concentration of the drugs in the calibra-

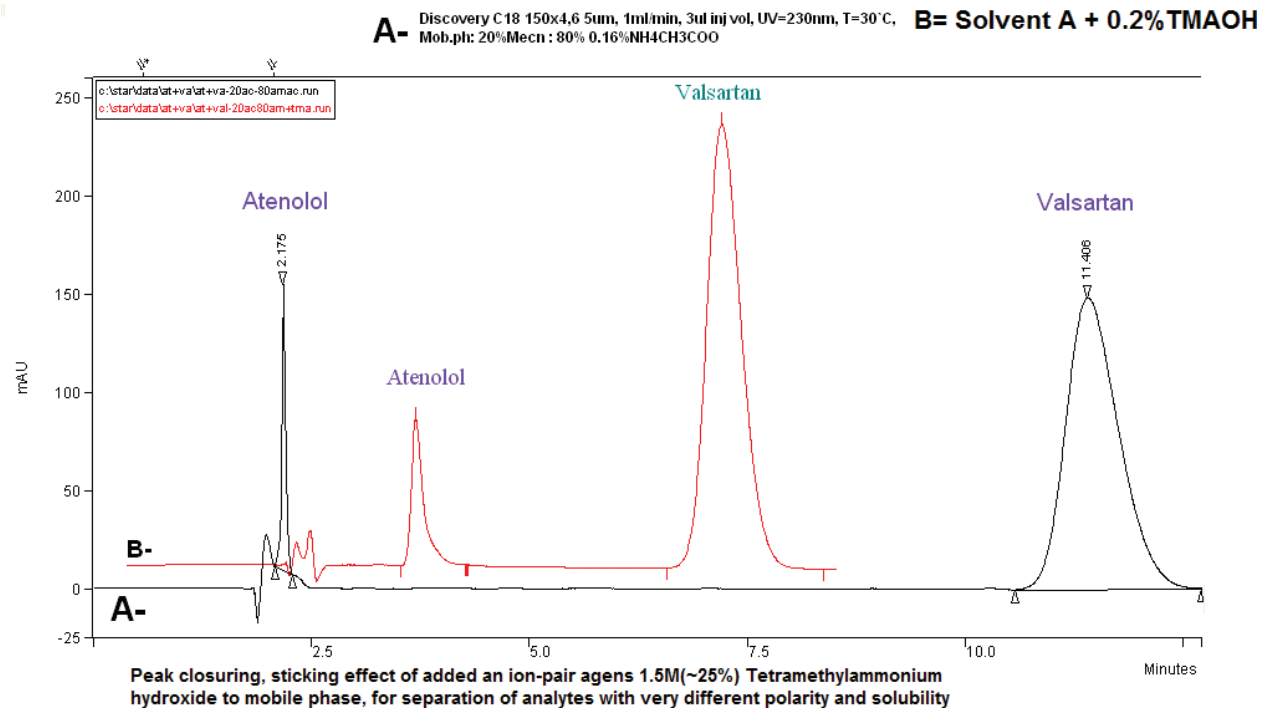

Figure 3. Elution profiles obtained for test samples prepared of Valsartan + Atenolol tablets (80 + 100) mg using mobile phases: **a**) 20% acetonitrile and 80% of 0.16% ammonium acetate (V/V); **b**) 20% acetonitrile, 80% of 0.16% ammonium acetate and 0.2 % of 1.5 M tetramethylammonium hydroxide (V/V). Chromatographic conditions: Shimadzu Nexera XR UPLC system, C18 chromatographic column Discovery C18 (4.6 mm i.d. × 150 mm, 5 µm), flow rate 1.0 mL/min, column temperature 30 °C.

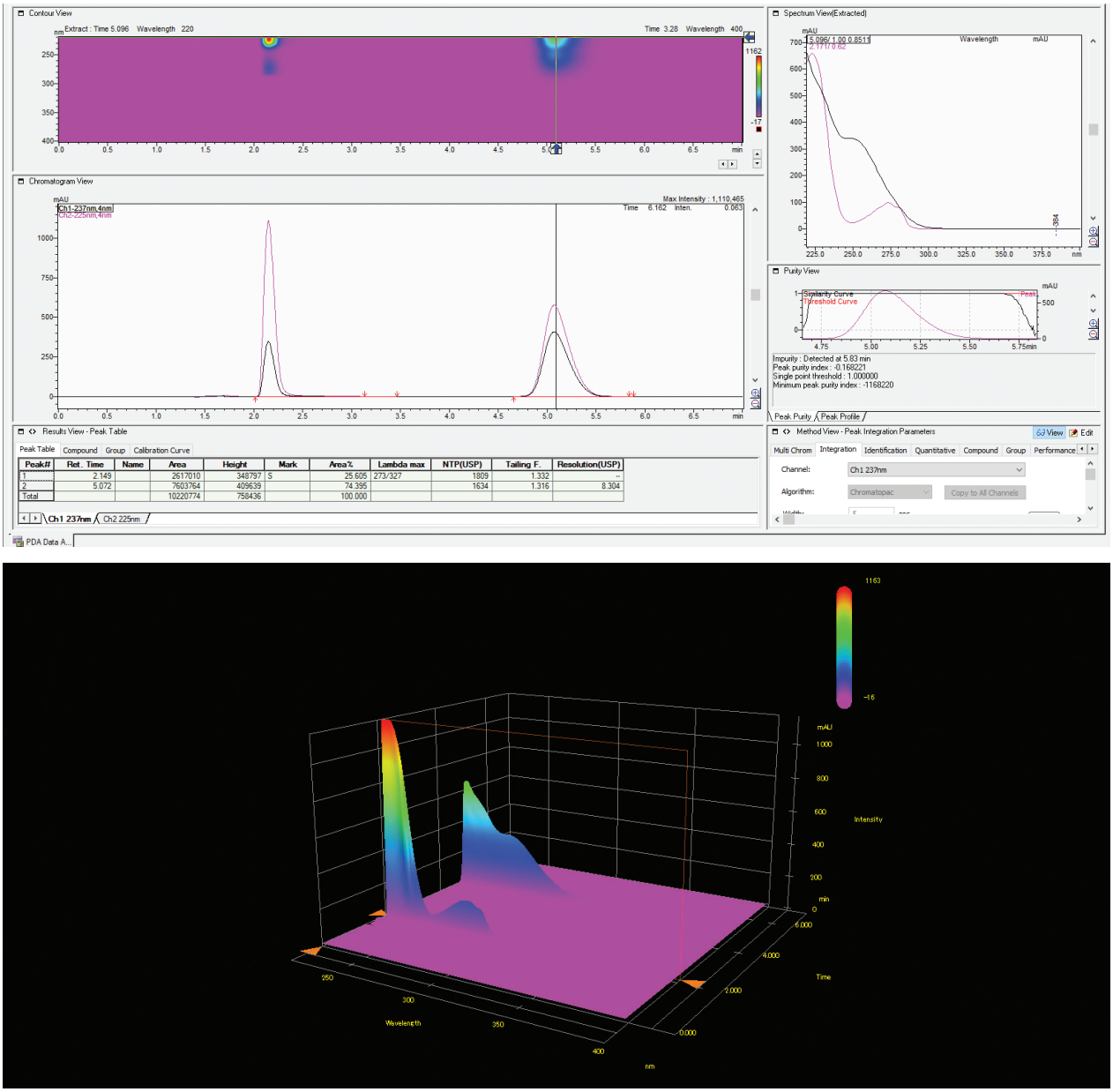

Figure 4. Chromatogram obtained using Shimadzu Nexera XR UPLC system and mobile phase 20% acetonitrile, 80% of 0.16% ammonium acetate and 0.2% of 1.5 M tetramethylammonium hydroxide (V/V), column Discovery C18 (4.6 mm i.d. × 150 mm, 5 µm) at 2 wavelengths 225 nm and 237 nm (first figure), with 3-D UV contour diagram extracted analytes UV spectra and peak purity (second figure).

tion curves and indicate high sensitivity of the proposed HPLC method.

Accuracy and precision

Intra-day and inter-day % RSD values lower than 2% clearly assuring that this method was found to be fairly precise and reproducible (Tables 1–4). Regarding accuracy, a known amount of the standard drug was added to the fixed amount of preanalyzed sample solution. % recovery was calculated by comparing the area before and after addition of the standard drug. The high value of recoveries obtained for valsartan and atenolol indicates that the proposed method was found to be accurate.

Table 1. Intra-day and inter-day precision for the HPLC determination of valsartan.

Day	Intra-day precision		Inter-day precision	
	Mean	RSD %	Mean	RSD %
1	99.01	0.451	100.91	0.314
2	100.12	0.543	99.24	0.382
3	100.98	0.385	100.42	0.624

*Each value is represented as a mean±SD of observations (n=5), SD: Standard Deviation, RSD: Relative Standard Deviation.

Robustness

The robustness of the developed method was evaluated by small deliberate changes in method parameters such as flow rate (+10%) and temperature of column (± 7%).

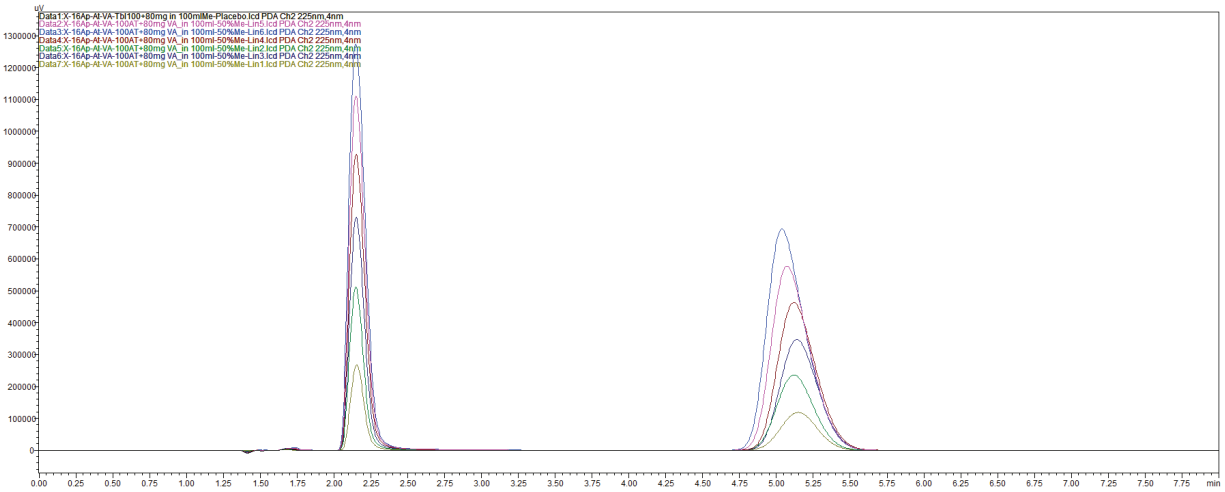

Figure 5. Chromatogram obtained using final established, optimized and validated chromatographic method at wavelength 225 nm.

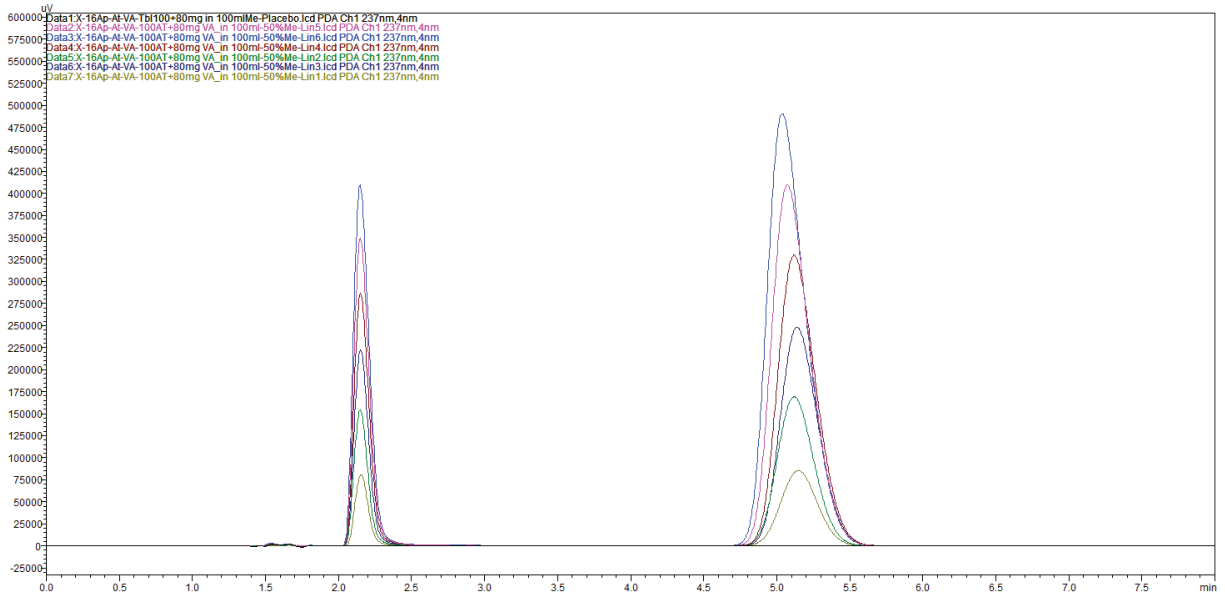

Figure 6. Chromatogram obtained using final established, optimized and validated chromatographic method at wavelength 237 nm.

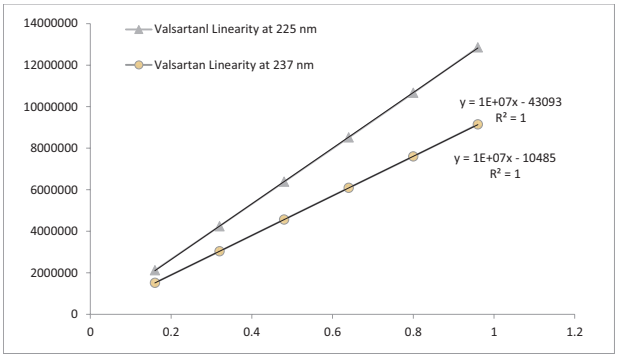

Figure 7. The calibration curves of valsartan.

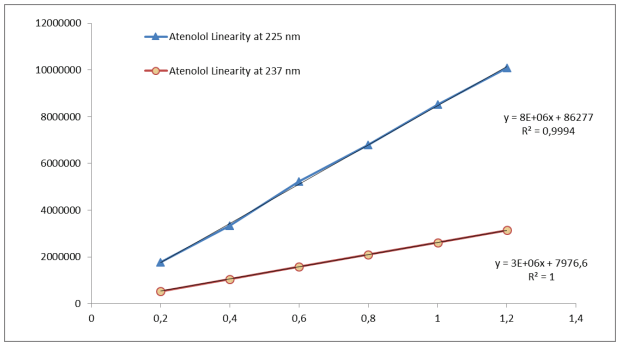

Figure 8. The calibration curves of atenolol.

The % RSD values of robustness which is less than 2% reveals that the proposed method is robust. The results of robustness study results are shown in Tables 5, 6.

Even though the small changes in the conditions did not significantly effect on retention time of valsartan and atenolol.

Methanol and acetonitrile are the most broadly used solvents in most analytical methods, and it is worth mentioning that methanol and acetonitrile are rated by the U.S. Environmental Protection Agency as hazardous solvents, given their inherent toxicity and the fact that their disposal necessitates specialized treatment steps, particularly for aceto-

Table 2. Intra-day and inter-day precision for the HPLC determination of atenolol.

Day	Intra-day precision		Inter-day precision	
	Mean	RSD %	Mean	RSD %
1	99.75	0.325	101.19	0.497
2	101.02	0.612	99.36	0.341
3	100.58	0.285	100.55	0.614

*Each value is represented as a mean±SD of observations (n=5), SD: Standard Deviation, RSD: Relative Standard Deviation.

Table 3. Accuracy study for the HPLC determination of valsartan.

Model	The amount of valsartan, %		Found,% to predetermined,
	Predetermined quantity,	Found quantity,	
Solutions	$X_i=(m_i/m_{rs})$ 100 %	$Y_i=(S_i/S_{rs})$ 100 %	$Z_i = (Y_i/X_i)\cdot 100\%$
M1	70.02	70.10	100.11
M2	80.51	80.75	100.30
M3	89.87	90.03	100.18
M4	95.09	95.31	100.23
M5	100.01	99.78	99.77
M6	104.91	105.26	100.33
M7	110.45	110.85	100.36
M8	120.43	120.58	100.12
M9	130.00	130.27	100.21
Average, *Z*, %			100.18
Standard deviation, S_z, %			0.18
Confidence interval of convergence of results (actual)			0.41
$\Delta z = t(95\%,8)\cdot S_z = 2.3060\cdot S_z$, %			
Critical value for the convergence of results			Performed
$\Delta \leq max\Delta_{As} = 2.4\%$			(< 2.4)
Systematic error $\delta=\lvert Z-100\rvert$, %			0.18
Criterion of significance of systematic error			Performed
$\delta \leq max\ \delta\%$			(< 0.77)
The general conclusion about the technique:			Correct

Table 4. Accuracy study for the HPLC determination of atenolol.

Model	The amount of atenolol, %		Found,% to predetermined,
	Predetermined quantity,	Found quantity,	
Solutions	$X_i=(m_i/m_{rs})$ 100 %	$Y_i=(S_i/S_{rs})$ 100 %	$Z_i = (Y_i/X_i)\cdot 100\%$
M1	70.01	70.09	100.11
M2	80.34	80.81	100.59
M3	89.96	90.12	100.18
M4	95.15	95.29	100.15
M5	100.01	99.79	99.78
M6	104.96	105.19	100.22
M7	110.55	110.79	100.22
M8	120.14	120.19	100.04
M9	130.00	130.27	100.21
Average, *Z*, %			100.17
Standard deviation, S_z, %			0.21
Confidence interval of convergence of results (actual)			0.48
$\Delta z = t(95\%,8)\cdot S_z = 2.3060\cdot S_z$, %			
Critical value for the convergence of results			Performed
$\Delta \leq max\Delta_{As} = 2.4\%$			(< 2.4)
Systematic error $\delta=\lvert Z-100\rvert$, %			1.17
Criterion of significance of systematic error			Performed
$\delta \leq max\ \delta\%$			(< 0.77)
The general conclusion about the technique:			Correct

Table 5. Results of the study of robustness for the HPLC determination of valsartan.

Conditions of analysis	Retention time, min
Standard conditions	5.07
flow rate 1.1 mL/min, (+10 %)	4.69
flow rate 0.9 mL/min, (-10 %)	5.62
temperature of column 28 °C	5.25
temperature of column 32 °C	4.98

Table 6. Results of the study of robustness for the HPLC determination of atenolol.

Conditions of analysis	Retention time, min
Standard conditions	2.15
flow rate 1.1 mL/min, (+10 %)	1.98
flow rate 0.9 mL/min, (-10 %)	2.35
temperature of column 28 °C	2.21
temperature of column 32 °C	2.09

nitrile, where detoxification through chemical treatment has to be carried out because traditional disposal (i.e., through combustion) produces a highly toxic compound (hydrogen cyanide). Analytical eco-scale is a semi-quantitative assessment tool commonly used for examining the greenness of analytical methods in a comparative manner. It is based on assigning a numerical score, penalty points, for every step in the whole analytical method that may affect the green system such as solvents, their amounts, energy consumption, occupational risk and waste generated hazards (Gałuszka et al. 2012; Goswami et al. 2018; Karamad et al. 2019).

The analytical eco-scale total score is then calculated by subtracting all these penalty points form 100 (the score of ideal green procedure). A score more than 75 represents excellent green analysis, from 75–50 represents acceptable green analysis, and less than 50 represents inadequate green analysis (Korany et al. 2017). Table 7 summarizes the results of proposed method found to be an excellent green analysis with a score of 84.

Table 7. Analytical eco-scale for greenness assessment of the proposed chromatographic method.

Parameters	Penalty points (PP)
Reagents	
Methanol	6
Acetonitrile	6
Energy consumption	1
Occupational hazards	0
Waste	3
Total penalty points (PP)	16
Analytical Eco-scale score	84
Comment	Excellent green analysis

Conclusion

A novel fast, simple and green but selective, accurate, precise and robust HPLC-UV method for simultaneous determination of valsartan and atenolol in newly formulated dosage form was developed and many possible variations of the same were suggested.

The developed method for the simultaneous quantification of valsartan and atenolol from solid dosage formulations offers simplicity essential for quality control of a large number of samples in short time intervals, which is necessary for routine analysis. The concept of mobile phase composition was evaluated and confirmed on different chromatographic systems. The C18 columns proved to be applicable due to make a shorter run time of analyses. Furthermore, the developed method showed good results for the tested validation

parameters, i.e. it is selective, accurate, linear and precise, and is thus suitable to be used for the simultaneous quantification of valsartan and atenolol in their challenging binary mixture.

This work was also focusing on the implementation of sustainable chemistry by replacing conventional solvents in method with less hazardous and greener ones without disrupting method performance. The method was subjected to greenness profile assessment.

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Supplementary material 1

Supplementary data

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