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Research Article

RP-HPLC Method for Estimation of Valsartan in Solid Oral Dosage Forms

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Abstract

A simple, specific, accurate and precise reverse phase high performance liquid chromatography (RP-HPLC) method was developed for the estimation of valsartan in solid oral dosage form. The chromatographic separation of valsartan was achieved under the following conditions: mobile phase containing acetate buffer (pH4.6): acetonitrile: methanol (38:24:38 %, v/v); ODS C18 (250 mm × 4.6 mm, 5 µm) analytical column in isocratic mode; room temperature and diode array detector at 248 nm. The compounds were eluted at a flow rate of 1.2 ml min^{-1}. The retention time of valsartan was found to be 4.6±0.06 min. Different analytical performance parameters such as specificity, linearity, precision, accuracy, limit of detection (LOD), limit of quantification (LOQ), robustness and ruggedness were evaluated according to ICH Q2R1 guidelines. Linearity was detected in the concentration range of 10-30 µg ml^{-1} for the drug. The maximum and minimum recovery were found to be 99.95% and 99.57%, respectively. LOD and LOQ for valsartan were 0.17µg ml^{-1} and 0.56µg ml^{-1}, respectively. Peak purity of the drug was 0.999. The method developed so far was free from interferences due to excipients present in the formulation. Thus, this analytical method was found suitable for routine quality control analysis.

Keywords: Valsartan, RP-HPLC, Analytical method development, Validation

1. Introduction

Chemically, valsatran is (2S)-3-methyl-2-[N-({4-[2-(2H-1,2,3,4-tetrazol-5-yl)phenyl] phenyl} methyl) pentanamido] butanoic acid (Fig. 1).[1]

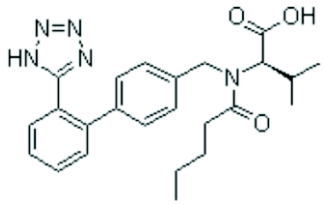


Fig. 1. Chemical structure of valsartan

AT_1-receptor antagonists or sartans, are a group of pharmaceuticals that modulate the renin-angiotensin-aldosterone system, with particularly high affinity for the type I angiotensin receptor (AT_1). By blocking the action of angiotensin, valsartan dilates blood vessels and reduces blood pressure.[2] It is an angiotensin receptor blockers that selectively inhibits the binding of angiotensin- II to AT_1, which is found in many tissues such as vascular smooth muscles and the adrenal glands. This effectively inhibits the AT_1-mediated vasoconstrictive and aldosterone-secreting effects of angiotensin-II and results in a decrease in vascular resistance and blood pressure. Valsartan is selective for AT_1 and has virtually no affinity for AT_2. Inhibition of aldosterone secretion may inhibit sodium and water reabsorption in the kidneys while decreasing potassium excretion. Valsartan is used in the treatment of hypertension, to lower blood pressure. Lowering blood pressure reduces the risk of fatal and nonfatal cardiovascular events, primarily strokes and myocardial infarctions. It is used in the treatment of heart failure, and it significantly reduces hospitalization for heart failure. It reduces cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction.[3] It has an oral bioavailability of 25% and is available in tablet dosage forms. An accurate and precise analytical method is important for the estimation of drug content in the dosage forms. The objective of this study is to develop a suitable, reliable and cost effective method for the estimation of valsartan in oral dosage forms.

2. Materials and Methods

2.1. Materials

Valsartan was received as a gift sample from Alembic Ltd., Vadodara, Gujrat, India. HPLC grade Methanol (Merck), HPLC grade Acetonitrile (Merck), HPLC grade water (Merck), Glacial acetic acid (Fisher scientific), HPLC grade and Analytical reagent grade sodium acetate anhydrous (Fisher scientific) were used in this study.

2.2. Method development and optimization of chromatographic conditions

Shimadzu HPLC system was used for the analysis of valsatran. The column used for chromatographic separation was ODS C18 (250mm × 4.6mm, 5µm) (Spincotech Pvt. Ltd., Japan). The mobile phase contained a mixture of acetate buffer (pH4.6): acetonitrile: methanol (38: 24: 38%, v/v), filtered through 0.45µm filter paper and deaerated in ultra sonic bath sonicator. The analytical wave length was set at 248 nm. Mobile phase was pumped in isocratic mode (LC-20AD, UFLC Shimadzu, Japan) at a flow rate of 1.2ml min^{-1}. SPD-M20A diode array detector (Shinadzu) was used in this analysis. Rheodyne injector (P/N 7725i) was used for the sample inputs. The separation was carried out at room temperature.

2.3. Preparation of standard solution

Accurately, 10 mg of valsartan was weighed and transferred into a 100 ml volumetric flask. The drug was dissolved in 30 ml of mobile phase and the volume was made up to100 ml with mobile phase. Ten millilitres of this solution was taken in a 50 ml volumetric flask and the volume was adjusted to the mark with mobile phase. Thus, a standard strength of 20μg/ml was obtained.

2.4. Preparation of sample solution

Twenty Valzaar® tablets each containing 80mg valsartan were weighed, average weight was calculated and the tablets powdered. A quantity of powder equivalent to 80mg valsartan powder was taken and dissolved in 50ml of mobile phase and was sonicated for 15min. Then, it was shaken and the volume was adjusted up to 100 ml with mobile phase. Subsequently, the solution was filtered. From the filtrate, 5ml sample was withdrawn and diluted to 50ml with mobile phase. Thereafter, 5ml diluted sample was pipetted out and the

volume was adjusted to 20ml with the mobile phase.

3. Results and Discussion

HPLC method was validated for the estimation of valsartan in Valzaar 80 mg tablets. The composition, pH and the flow rate of the mobile phase were optimized. A mobile phase consisting of acetate buffer (pH 4.6): acetonitrile: methanol (38: 24:38%, v/v), set at a flow rate of 1.2 ml min^{-1} was selected for use for further studies after several preliminary investigatory chromatographic runs. A typical chromatogram obtained from the analysis of drugs using the developed method is shown in Fig. 2. Under the experimental conditions described earlier, all the peaks were well-defined and free from tailing. The effects of small deliberate changes in the mobile phase composition, pH and flow rate were evaluated as a part of testing for method robustness.

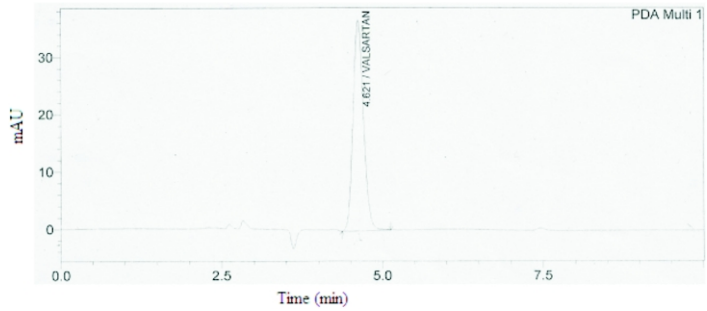


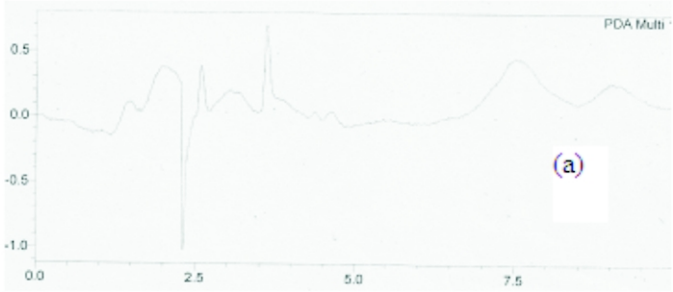
Fig. 2. A typical chromatogram of standard valsartan (20µg ml^{-1})

The analytical method was validated with respect to parameters such as specificity, linearity, precision, and accuracy, limit of detection (LOD), limit of quantitation (LOQ), and robustness and ruggedness.[4-8]

The method specificity was assessed by comparing the chromatograms obtained from the drug and the most commonly used excipients mixture with those obtained from blank (excipients solution in water without drug). The method was specific as none of the excipients nor did the blank interfere with the analytes of interest (Table 1). As evidence, the specific chromatograms are shown in Fig. 3a-c and Fig. 3d-e.

Table 1. Specificity studies

Drug	Sample	Area	Peak purity
Valsartan	Blank	None	0.00
	Placebo	None	0.00
	Standard	417255	1.00
	Placebo & Analyte	412368	0.99
	Sample	412384	0.99



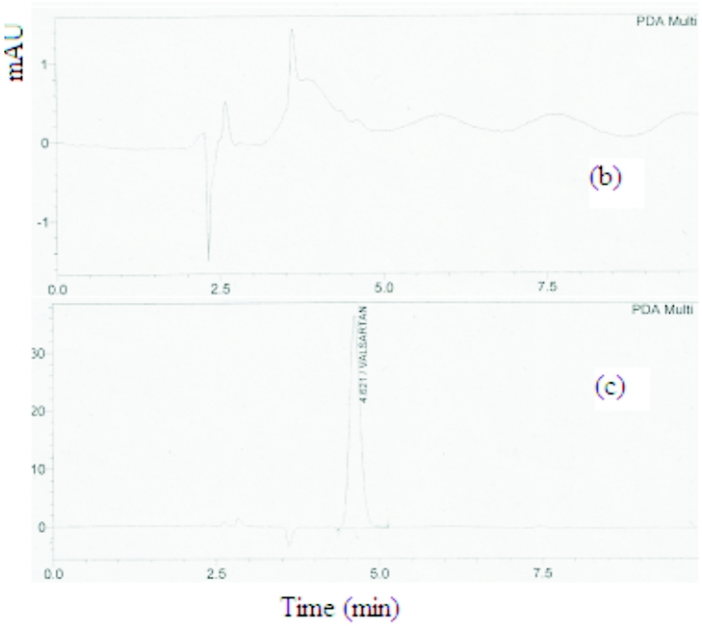


Fig. 3a-c. A typical chromatogram of (a) blank solution; (b) placebo solution; (c) standard solution of valsartan in mobile phase

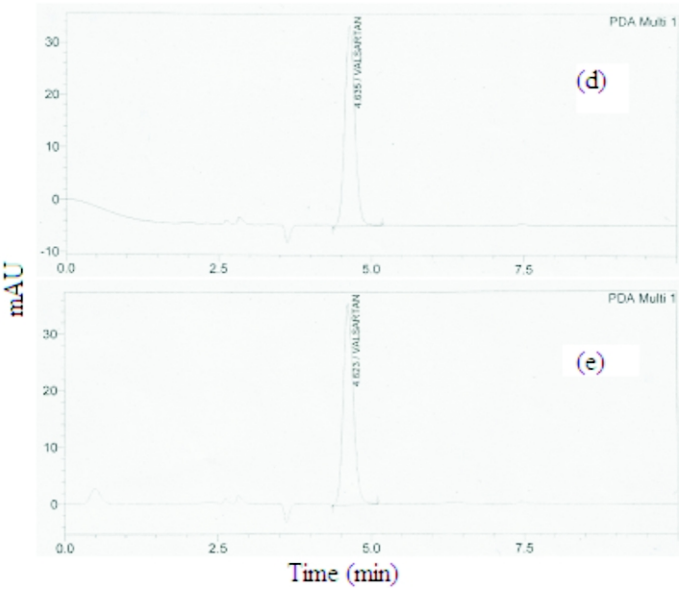


Fig. 3d-e. A typical chromatogram of (d) placebo and analyte solution and (e) sample solution of valsartan in mobile phase

The linearity was established by least squares linear regression analysis of the calibration curve. The calibration curves were linear over the concentration range of 10-30µg ml^{-1}. Peak areas were plotted as a function of their respective concentrations and linear regression analysis was performed on the resultant curves. Correlation coefficients were found to be 0.999. The results are given in Table 2.

Table 2. Linear regression data for calibration curves

Parameters	Valsartan
Linearity Range (μg ml^{-1})	10-30
Correlation coefficient	0.999
Slope	20888.12
Intercept	-1.61286

Intra-day precision was investigated by injecting six replicate samples of the same batch. Each of the samples was injected on the same day. The % RSD obtained for valsartan was found to be 0.61. Inter-day precision was assessed by injecting the three samples over six consecutive days. The % RSD obtained for valsartan were found to be 0.89. LOD and LOQ were determined by calibration curve method. LOD and LOQ were 0.17 and 0.56µg ml^{-1}, respectively.

Recovery study was carried out by applying the method to a drug sample to which a known amount of standard corresponding to 50, 100 and 150% of label claim was added. At each level of the amount added, three determinations were performed. The maximum and minimum recoveries obtained were 99.95% and 99.57%, respectively. The results are given in Table 3.

Table 3. Detailed recovery study protocols and results along with relative standard deviation (%RSD)

Recovery level %		Placebo added (mg)	Amount standard added (mg)	Amount standard added with respect to potency(mg)	Amount recovered (mg)	Recovery %	% RSD
50	1	80.15	40.02	39.98	39.96	99.95	0.10
	2	80.68	40.12	40.08	39.99	99.78	
	3	80.69	40.05	40.01	39.99	99.95	
100	1	80.60	80.13	80.05	79.97	99.90	0.04
	2	80.66	80.14	80.05	79.94	99.85	
	3	80.68	79.18	79.10	78.96	99.82	
150	1	80.65	120.21	120.09	119.96	99.89	0.16
	2	80.64	120.06	119.94	119.56	99.68	
	3	80.67	120.11	119.99	119.47	99.57	

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. Robustness of the method was investigated under a variety of conditions including changes in composition of buffer in the mobile phase, mobile phase buffer pH, and changes in wavelength and flow rate. RSD (%) of assay was calculated for each condition. The degree of reproducibility of the results obtained as a result of small deliberate variations in the method parameters proved that the method was robust. The results are cited in Table 4.

Table 4. Robustness studies

Parameters	Tailing factor	Theoretical plates	Retention Time (min^{-1})	Change in assay value from mean assay value (%)
Flow rate (ml^{-1})				
1.085	1.12	3817	5.01	0.41
1.320	1.14	3819	4.20	0.22
Buffer: Acetonitrile: Methanol				
40:22:38	1.12	3715	4.93	0.23
36:26:38	1.14	3845	4.37	0.51
40:24:36	1.15	3721	4.89	0.35
36:24:40	1.13	3814	4.43	0.26
Buffer pH				
4.4	1.17	3814	4.57	0.42
4.8	1.28	3796	4.59	0.63
Wavelength (nm)				
245	1.26	3654	4.63	0.81
251	1.31	3751	4.66	0.62

The ruggedness of the method was assessed by comparison of the intra-day and inter-day assay results for valsartan that had been performed by two analysts, on two different days. The % RSD values for assays performed in the same laboratory by two analysts on two different days did not exceed 2, indicating the ruggedness of the method. The results are given in Table 5.

Table 5. Ruggedness studies

Parameters	Peak area	% RSD, $n=6$
Analyst-1	438521	0.61
Analyst-2	448512	0.22
Day-1	445561	0.31
Day-2	438923	0.37

The proposed RP-HPLC method was applied to the simultaneous estimation of valsartan in Valzaar 80mg tablets and drug content in each sample was calculated by comparison with the appropriate standard solution of the drug. No interference due to excipients was detected. The assay value was found to be 99.75%.

4. Conclusion

RP-HPLC method enabled the quantitation of valsartan with good accuracy and precision, whether in laboratory prepared samples or in solid pharmaceutical dosage forms. Good recoveries were obtained in all cases. The proposed methods could be applied efficiently for determination of valsartan in oral dosage form with satisfactory precision. This method is considered simple, reliable, and selective providing results with satisfactory accuracy, and precision with lower limits of detection and quantification, thus making it more specific and sensitive. Moreover, the shorter duration of analysis for valsartan makes this analytical method suitable for routine analysis of pharmaceutical dosage forms.

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