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Review Article on Valsartan

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ABSTRACT

A simple, sensitive, rapid and reproducible HPLC method has been developed and validated for Calibration determination of Valsartan in bulk and in pharmaceutical formulation by applying Quality intentionally. For development of HPLC method for Valsartan various trials are performed by using Design Expert software by applying 3 level factorial designs. Quantitative method development by optimization from trials intentionally Expert software. The Optimized method Desirabilityis0.998 for Mobile Phase ACN: Phosphate Buffer (65:35) in3.5 pH at maximum Wavelength 274nm at column oven temperature 40°C. The flow of mobile phase was adjusted 1.0 ml/min. and therefore the injection volume 10 µl. Optimised Standard curve showed a parametric statistic is 0.998. Retention time was found to be 4.6 min. the half of recovery was found to be within the bounds of the acceptance criteria with average recovery of 99.4 you take care of Valsartan. The tactic was validated as per ICH guidelines. The precision and repeatability results showed % RSD but 2%. The developed method was successfully validated in consistent with ICH guidelines. Hence, these methods are often conveniently adopted for the routine analysis in internal control laboratories.

KEYWORDS: *Quality intentionally, Valsartan, HPLC, Design Expert Software*

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INTRODUCTION

Valsartan may be a non-peptide compound, chemically describes as "(S)-3-methyl-2-(N-{[2′-(2H-1,2,3,4-tetrazol-5-yl)biphenyl-4-yl]methyl}-pentanamido)-butanoic acid", (Val, Figure 1) used as angiotensin II receptor antagonist having high specificity for AT1 subtype1. Angiotensin II receptor antagonists, also referred to as angiotensin receptor blockers (ARBs) or sartans, are a gaggle of pharmaceuticals that modulate the renin-angiotensin-aldosterone system. Currently, there are seven ARBs (losartan, valsartan, candesartan, irbesartan, eprosartan, telmisartan and olmisartan) which are approved by USFDA and utilized in preventing first occurrence of fibrillation than beta-blocker (atenolol) or calcium antagonist (amlodipine) therapy2. Hydrochlorothiazide chemically describes as "6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide" (HCT, Figure 1b) is employed as diuretic in binary combination with the cardiovascular agents so as to extend their effects3-4. Several HPLC methods for the estimation of ARB alongside HCT4-6 were reported during last 20 years. Simultaneous determination of Val and HCT using various spectrophotometric methods7-11, HPLC12-16, HPTLC15,17, and capillary electrophoresis18 is documented. Additionally, HPLC-MS–MS was applied for the quantification of both drugs in human plasma.

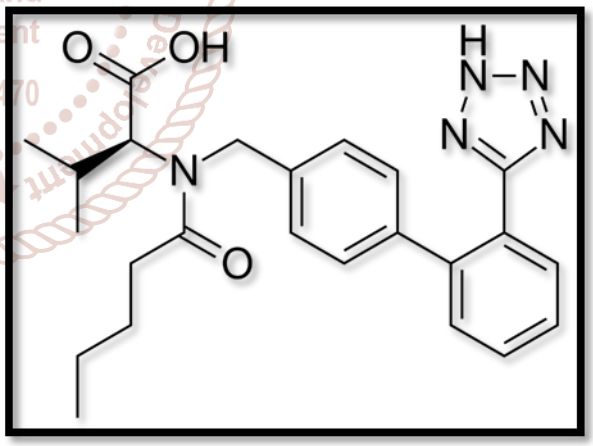

Figure 1: Structure of Valsartan

Although a couple of published methods, are stability indicating developed on random basis by modifying one parameter ("One parameter at a time", OPAT). ICH (ICH, Q8-R1, R2) guideline states "Quality by Design" (QbD) as "a systematic approach to development that begins with predefined objectives and emphasizes product and process understanding and process control, supported sound science and quality risk management" 22,23. Literature survey reveals that a non-stability indicating HPLC method16 was developed utilizing design of experiment protocol (DoE) for estimation of valsartan. The parameters studied were pH (2.8 to 3.2), flow-rate (0.8 to 1.2 ml/min) and detection wavelength (248 to 252 nm). Careful examination indicates that the pH and wavelength are producing moderate slight

effect on the height area, tailing factor and theoretical plate count (perturbation plots and equation)16. The composition of mobile phase was kept constant. Since the valsartan may be a BCS class II drug has low solubility, a correct selection of mobile phase is requires, while HCT has different characteristic. Keeping these parameters in mind this method was developed. Pharmaceutical industries are paying more attentions on the event of analytical methods utilizing "Quality by Design" (QbD). Robust analytical methods which may deliver the intended performance are often developed and validated utilizing the concepts of "Analytical Quality by Design"(AQbD). AQbD uses a scientific approach to make sure quality by developing a radical understanding of interaction of various component and process involved in analysis. The tactic development and validation utilising different aspects of AQbD are often improved and optimized for the routine analysis, internal control and analysis of product under development. Several analytical methods having deficiencies are still used for the standard control and analysis is often improved using the AQbD. The experimental conditions with different variables (two or more) are often optimized using "Design of experiments" (DoE) 23-29. this work was aimed to develop, optimize and validate a sensitive, specific, precise, accurate and stability indicating method for the estimation of Val and HCT (in presence of possible degraded products) in active pharmaceutical ingredient (API) and tablets utilizing "Analytical Quality by Design".

Method:

1. Preliminary Analysis of Drug

A. Description

Colour and texture of Valsartan was compared with reported characters mentioned in drug bank.

B. Solubility

Solubility of Valsartan decided in various solvents like methanol, ethanol and Acetonitrile.

C. UV Analysis

UV analysis was administered by scanning the answer of Valsartan at 200-400 nm.

2. Design of Experiment

2-level factorial designs by Design expert 8 Software.

Two-level factorial design is an experimental matrix that has limited application in factorial design when the factor number is above 2 because the amount of experiments required for this design (calculated by expression N = 2k, where N is experiment number and k is factor number) is extremely large, thereby losing its efficiency within the modelling of Linear functions.

Selection of Dependant factors

1. Mobile Phase
2. pH of Mobile phase

Selection of Independent factors

1. Retention Time
2. Area
3. Theoretical Plate
4. Asymmetry

Columns used

- C18 Column

Following mobile phases selected

- Water : Methanol
- Water : Acetonitrile
- Phosphate Buffer : Acetonitrile

Miscellaneous Factorial designs facilitate only one mobile phase at a time:

- Water : Acetonitrile
- Change pH Range: 4-6
- Change Mobile phase proportion Range: 35-65% (Consider Acetonitrile)
- Change flow rate range: 0.9 to 1mL/min

When all of above ranges put in 2 Level Factorial design. It gave 08 run at different pH and Mobile phase proportion. Follow same procedure for every mobile phase. Column C-18 has four mobile Phases with 24 run each mobile phase. After completion of all trails software give one optimize best value for every column. Optimization means finding an alternate with the foremost cost effective or highest achievable performance under the given constraints, by maximizing desired factors and minimizing undesired ones. Ascompared, maximization means trying to achieve the very best or maximum result or outcome without reference to cost or expense.

3. Preparation of mobile phase

65 ml of HPLC grade Methanol was added to 35 ml of Water i.e. in 65: 35 v/v proportions. The pH was adjusted to 4 with phosphoric acid .the answer was filtered through 0.45µ membrane filter then sonicated in sonicator bath for 10 min.

4. Preparation of stock solutions of Valsartan

Stock solution was prepared by dissolving 10 mg Valsartan in Acetonitrile then diluted with Acetonitrile in 10 ml of volumetric flask to urge concentration of 1000 µg/ml. From the resulting solution 0.4 ml was diluted to 10 ml with Acetonitrile to get concentration of 40 µg/ml of Valsartan and labelled as standard stock Valsartan.

5. Selection of detection wavelength

From the quality stock solution further dilutions were done using Methanol and scanned over the range of 200-400 nm and therefore the spectra were overlain. It had been observed that drug showed considerable absorbance at 274 nm.

A. Optimization Result

Screening design for suitable chromatographic condition:

Determination of solvent system supported peak parameters. Methanol: water/ ACN: water and ACN: Ammonium Format Buffer, these three mobile phases were selected for screening study on C18 columns at pH 4.0 and 6.0. These mobile phases were screened by varying the organic phase composition from 40 to hour v/v. flow was varying form 0.9-1 ml/min.

Results of various trials, having organic phase composition 65 % v/v are shown in following tables.

Table 1.Trials performed on C18 column at mobile phase (65:35 v/v) with aqueous phase pH 4

Sr. no.	Composition	Observation	Remarks
1	Methanol: water	Less peak asymmetry but less theoretical plates	Satisfied
2	ACN: buffer	Less peak asymmetry with more theoretical plates and good retention time with greater peak height	Extremely Satisfactory
3	ACN: water	Greater peak Asymmetry and lower theoretical plates	Not satisfactory

Optimized chromatographic conditions

Mobile phase: Phosphate buffer: Acetonitrile (35: 65 v/v), pH of buffer: 4, Analytical column: C18 column Waters XBridge (4.6× 250mm id. particle size 5µm), UV detection: 274 nm, Injection volume: 10 µL, Flow rate: 1.00 mL min -1, Temperature: Ambient, Run time: 10 min

Effect of independent variables on retention time (X):

After applying experimental design, suggested Factorial Model was found to be significant with model F value of 52.03, p value but 0.005 and R2 value of 0.000. There's only a 0.01% chance that a "Model F-Value" this massive could occur thanks to noise. Values of twenty-two C.V. and adjusted R2 were 28.87 and 0.000 respectively. The model for response X (Retention time) is as follows:

The equation for Factorial model is as follows

Retention Time (X)= +8.24

Fig.2 shows a graphical representation of pH of buffer (B) and amount of ACN (A), while flow (C) is maintained constant at its optimum of 1 mL min-1.

Change in pH of buffer showed slightly change in retention time (X), also increase in amount of Acetonitrile showed decreases the retention time.

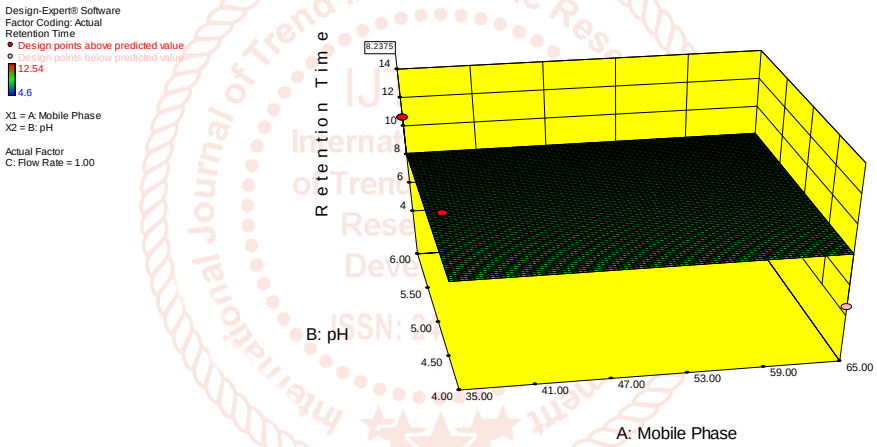

Fig.2Three-dimentional plot for retention time as a function of pH of buffer and amount of buffer. Constant factor (flow rate- 1mL min^{-1})

Fit summary: Quadratic model was suggested by the software.

ANOVA: ANOVA of developed 2 level factorial models for retention time (Y_1).

Values of "Prob > F" (p- value) but 0.0500 indicate model terms are significant.

During this case all factors are significant model terms. E

Table 2.Significance of *p* value on model terms of retention time

Source	Sum ofSquare	Df	MeanSquares
Model	0.000	0	
Residual	86.66	7	12.38
Cor Total	86.66	7	

Effect of independent variables on tailing factor (Y):

After applying experimental design, suggested Response Surface Linear Model was found to be significant with model F value of 1.19, p value but 0.005 and R2 value of 0.0000. There's only a 0.0001% chance that a "Model F-Value" this massive could occur thanks to noise. Values of twenty-two C.V. and adjusted R2 were 24.44 and 0.0000 respectively. The model for response

Y (Tailing factor) is as follows:

Y = +1.37

Fig.3. shows a graphical representation of pH of buffer (B) and amount of Acetonitrile (A), while flow (C) is maintained constant at its optimum of 1.0 mL min-1.

As increases in pH of buffer had antagonistic effect on response while increase in amount of Acetonitrile showed decreases the asymmetric factor.

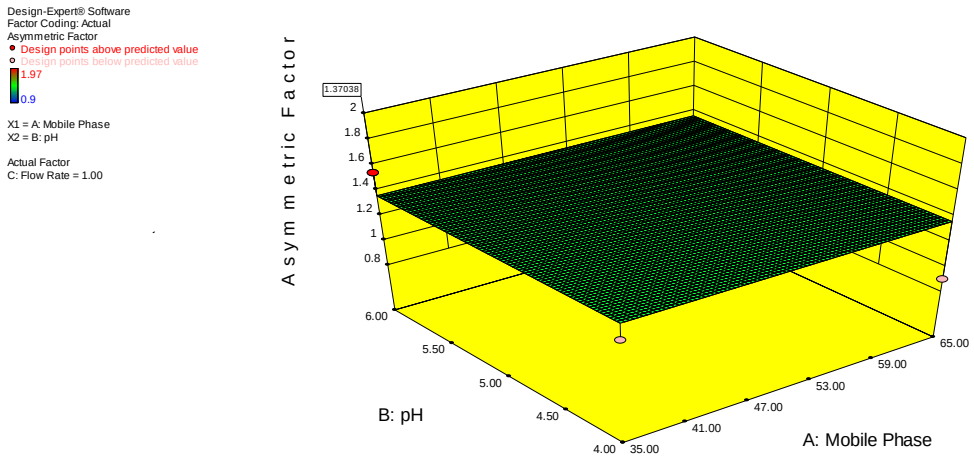

Fig.3 Three-dimentional plot for tailing factor as a function of pH of buffer and % v/v of buffer. Constant factor (flow rate- 1mL min^{-1})

Fit summary: Response Surface Linear Model was suggested by the software.

ANOVA: ANOVA of developed factorial model for tailing factor (Y).
Values of "Prob>F" (p-value) less than 0.0500 indicate model terms are significant.
In this case A, B are significant model terms.

Table 3.Significance of *p* value on model terms of tailing factor

Source	Sum ofSquare	Df	MeanSquares
Model	0.000	0	
Residual	0.87	7	0.12
Cor Total	0.87	7	

Effect of independent variables on theoretical plates (Z):
After applying experimental design, suggested Response Surface Quaratic Model was found to be significant with model F value of two .65, p value but 0.005 and R2 value of 0.000. There's only a 0.0001% chance that a "Model F-Value" this massive could occur thanks to noise. Values of twenty-two C.V. and adjusted R2 were 69.42 and 0.000 respectively. The model for response Z (theoretical plates) is as follows:
Z= +7289.13

Fig.4 shows a graphical representation of amount of methanol (A) and pH of buffer (B), while flow (C) is maintained constant at its optimum value 1mL min-1.

An increases in pH of buffer showed increase in number of theoretical plates (Z), while increase in amount of Acetonitrile showed increases response. Combination of amount of Acetonitrile and pH of buffer showed synergistic effect thereon.

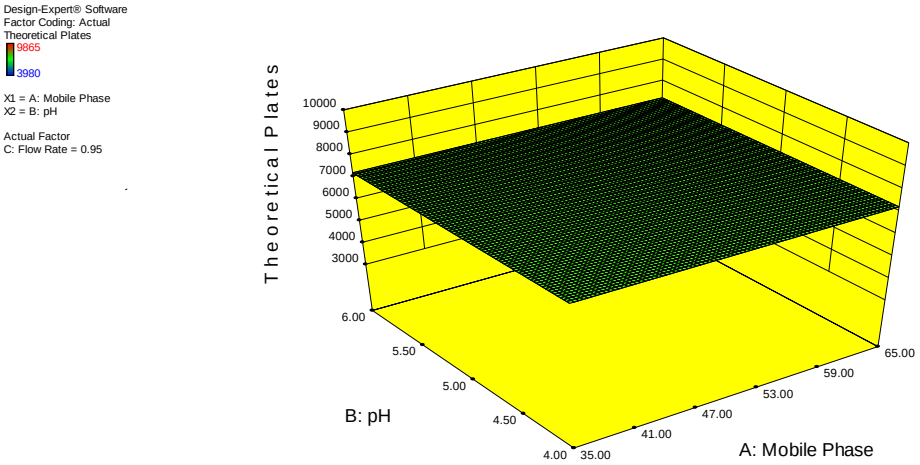

Fig.4Three-dimentional plot for theoretical plates as a function of pH of buffer and % v/v of buffer. Constant factor (flow rate- 1 mL min^{-1})

Fit summary: Factorial model was suggested by the software

ANOVA: ANOVA of developed CCD model for theoretical plates (Z).
Values of "Prob > F" (p- value) less than 0.0500 indicate model terms are significant.
In this case model is significant.

Table 4.Significance of *p* value on model terms of theoretical plates

Source	Sum ofSquare	df	MeanSquares
Model	0.000	0	
Residual	3.074E+007	7	4.392E+006
Cor Total	3.074E+007	7	

Validation:

1. Linearity:

Appropriate aliquots of ordinary Valsartan stock solutions (100µg/ml) were taken in several 10 ml volumetric flask and resultant solution was diluted up to the mark with Methanol to get final concentration of 10-50µg/ml. These solutions were injectedintochromatographicsystem.Thechromatogramswereobtainedandpeakarea decided for every concentration of drug solution and given in Table No. Calibration curve of Valsartan was constructed by plotting peak area vs applied concentration of and regression of y on x was computed. The slope, intercept, and coefficient of correlation were also determined and are shown in Figures no :5 The results show that excellent correlation exists between peak area and concentration of drugs within the concentration range which are presented.

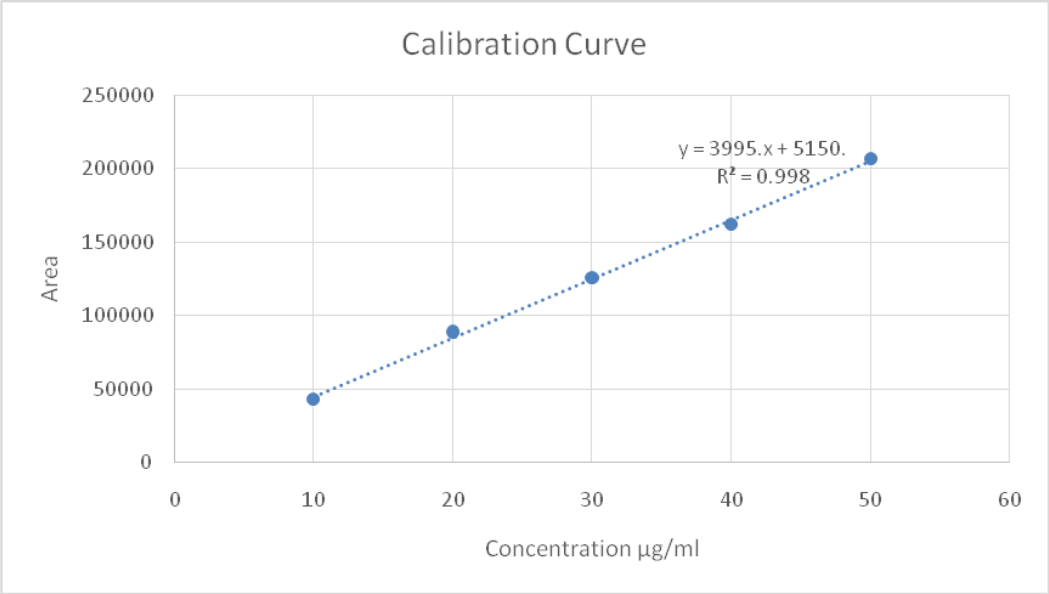

Fig 5.Calibration Curve of Valsartan

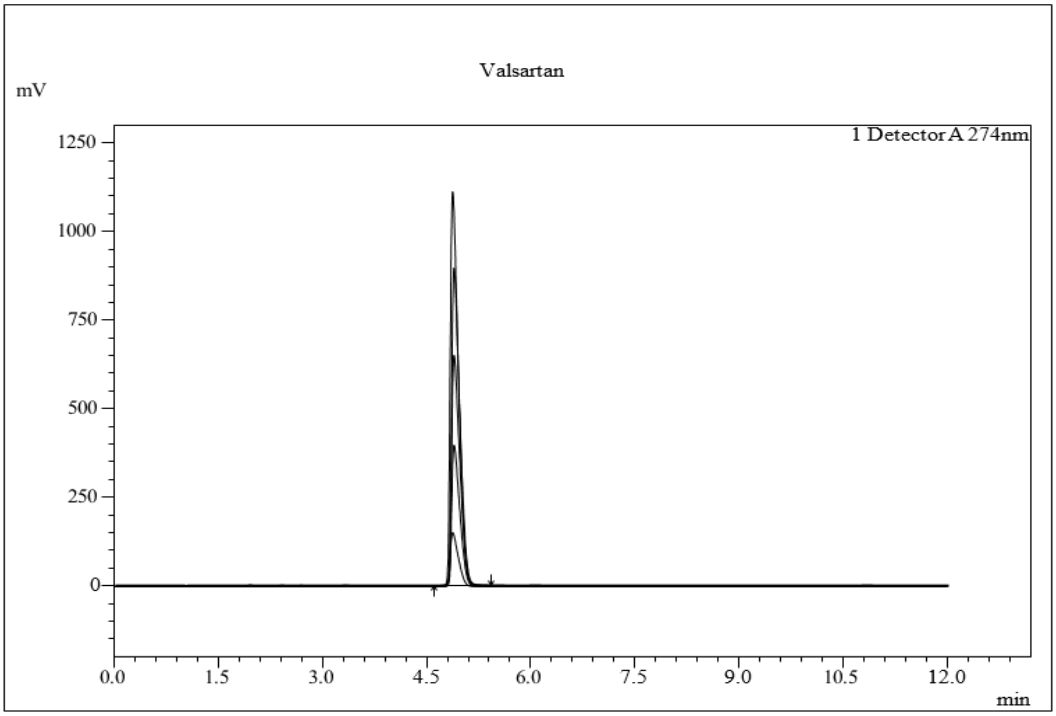

Fig 6. Overlain of Valsartan

Table no 5.Characteristic parameters of Valsartan for the proposed HPLC method.

Sr. No.	Parameter	Result
1	Calibration range (µg/ml)	10-50
2	Detection wavelength (nm)	274
3	Solvent (Acetonitrile: buffer)	60:40
4	Regression equation (y*)	y = 3995.3x + 5150.7
5	Slope (b)	5150.7
6	Intercept (a)	3995.3
7	Correlation coefficient(r2)	0.998
8	Limit of Detection (µg/ml)	0.0045
9	Limit of Quantitation (µg/ml)	0.0133

2. System Suitability:

System-suitability tests are an integral a part of method development and are wont to ensure adequate performance of the chromatographic system. Retention time (Rt), number of theoretical plates (N) and tailing factor (T) were evaluated for 6 replicate injections of the drug at a degree of 40 µg/ml.

3. Specificity:

Chromatogram of blank was taken as shown in Table no.6 Chromatogram of Valsartan showed peakataretention time of 2.910min.Themobilephase designed for the method resolved the drug very efficiently. The Retention time of Valsartan was 2.910 ± 0.0078min. The wavelength 277.8 nm was selected for detection because; it resulted in better detection sensitivity for the drug. The peak for Valsartan from the tablet formulation was Valsartan.

Table no 6.Specificity of Valsartan by HPLC method

Concentration	API Area	Tablet Area
40	163423	160988
40	162425	163246
40	164053	161289
40	163907	159328
40	160407	159598
Mean	162634	160423
SD	1439.17	1809.70
RSD	0.88	1.13

4. Sensitivity:

The sensitivity of measurement of Valsartan by use of the proposed method was estimated in terms of the limit of detection (LOD) and the limit of quantification (LOQ). The LOD and LOQ were calculated by the use of signal to noise ratio. In order to estimate the LOD and LOQ values, the blank sample was injected six times and the peak area of this blank was calculated as noise level. The LOD was calculated as 3 times the background level, while ten times the noise value gave the LOQ. LOD and LOQ were found to be 0.0045 and 0.0133 respectively.

5. Precision:

Demonstration of precision was done under two categories. The injection repeatability (System Precision) was assessed by using six injections of the standard solution of Valsartan and the % RSD of the replicate injections was calculated. In addition, to demonstrate the precision of method (Method Precision), six samples from the same batch of formulation were analysed individually and the assay content of each sample was estimated. The average fourth six determination was calculated along with the percentage RSD for the replicate determinations. Both the system precision and method precision were subjected for inter-day, intra-day and repeatability variations as reported in Table no..7 respectively.

Table no. 7. Intraday Precision of Valsartan at 274

Concentration	Peak Area		
	0 Hrs	2 Hrs	3 Hrs
40	159587	161879	159335
40	163423	164084	161078
40	162425	163986	163588
40	162153	161359	163606
40	160907	161288	162108
40	161407	160021	159764
Mean	161650	162103	161580
SD	1331.48	1616.95	1844.20
RSD	0.82	1.00	1.14

Table no. 8. Interday Precision of Valsartan at 235

Concentration	Peak Area		
	1 day	2 day	3 day
40	159587	160579	162784
40	163423	164984	160578
40	162425	162598	161588
40	162053	161359	163599
40	161907	161288	160108
40	163407	163938	164844
Mean	162134	162458	162250
SD	1407.98	1714.53	1825.15
RSD	0.87	1.06	1.12

Accuracy:

Recovery studies by the standard addition method were performed with a view to justify the accuracy of the proposed method. Previously analyzed samples of Valsartan (40µg/ml) were spiked with 80, 100, and 120 % extra Valsartan standard and the mixtures were analyzed by the proposed method.

Standarddeviationofthe%recoveryand%RSDwerecalculateda ndreportedin Table no.9 respectively.

Table no.9 Accuracy of Valsartan at 235 nm.

Sr. No.	Concentration	Peak Area	recovery%
1	80	163423	100.08
2	80	162425	100.20
3	80	162153	100.11
4	100	206226	99.99
5	100	206156	100.05
6	100	206215	100.12
7	120	247471	100.07
8	120	239848	99.98
9	120	238497	99.66

Robustness:

Robustness is a measure of capacity of a method to remain unaffected by small, but deliberate variations in the method conditions, and is indication so there liability of the method. a method is robust, if it sun affected by small changes in operating conditions. To determine the robustness of this method, the experimental conditions were deliberately altered at three different levels and retention time and chromatographic response were evaluated .One factor at a time was changed to study the effect .Variation of mobile phase composition (Acetonitrile: Water and Acetonitrile: buffer) and mobile phase flow rate by 1.0 ml/min had no significant effect on the retention time and chromatographic response of the 40 µg/ml solution, indicating that the method was robust. The results are shown in Table no.10& 11 respectively.

Table no. 10 Robustness of Valsartan at 274. Nm

Conc. (µg/ml)	Area	
	Acetonitrile: Buffer	Acetonitrile: Water
40	161879	12126
40	163084	12568
40	163986	12689
40	161359	12689
40	161288	12878
40	160021	12888
Mean	161936	12640
SD	1410.23	280.12
RSD	0.87	2.22

Table no. 11 Robustness of Valsartan at 274 nm and 265 nm

Conc. (µg/ml)	Area	
	274 nm	265 nm
40	162587	150815
40	163423	153579
40	163825	154284
40	162153	153968
40	159907	153277
40	161407	150589
Mean	162217	152752
SD	1426.41	1625.78
RSD	0.88	1.06

References:

[1] Khopkar SM. Basic Concept of Analytical Chemistry. 2nd ed. New Delhi: New Age International Ltd. Publishers; 1998. p. 1, 178-179.

[2] Christen GD. Analytical Chemistry. 5th ed. John Wiley and Sons; 2003. p. 35-42, 131-132.

[3] Skoog DA, Holler FJ, Crouch SR. Principle of Instrumental Analysis. 5th ed. Thomson Brooks/Cole.; 2004. p. 1-2, 678-688.

[4] Beckett AH, Stenlake JB. Practical Pharmaceutical Chemistry. Part-2. 4th ed. New Delhi: CBS Publishers and Distributors; 2002. p. 275-325.

[5] Chatwal GR, Sharma AK. Instrumental Methods of qualitative analysis. 5thed. Mumbai: Himalaya Publishing House; 2002. p. 2.149-2.184.

[6] handbook Pharmaspec, UV 1601 Series, Operation Guide, Shimadzu Spectrophotometer. Japan: Shimadzu Corporation Koyoto; 2001. p. 5.16, 8.2.

[7] Swarbrick J, Boylan JC. Encyclopedia of Pharmaceutical Technology. Vol-1. 3rd ed. New York: Marcel Dekker Inc.; 1997. p. 538-540.

[8] Skoog DA, Holler FJ, Nieman TA. Principles of Instrumental Analysis. 6th ed., Thomson Brooks/Cole.; 2007. p. 762-63,816-827.

[9] Dong MW. Modern HPLC for practicing scientists. New Jersey: John Wiley & Sons, Inc., Publication, Hoboken; 2006.p. 1-9.

[10] Sethi PD. High Performance Liquid Chromatography, quantitative chemical analysis of Pharmaceutical Formulations. 1st ed. New Delhi: CBS Publishers and Distributors; 2001.p. 3-11, 116-120.

[11] Weston A, Brown PR. High Performance Liquid Chromatography, and CE – Principles and practice. 1st ed. California: Academic Press; 1997. p. 1-4, 8-11, 24-26, 29-32, 71.

[12] Willard HH, Meritt LL, Dean JA, Settle F. Instrumental Method of study, 7th ed. Delhi: CBS Publishers and Distributors; 2001.p.14.

[13] Swadesh JK. HPLC Practical and Industrial Applications. 2nd ed. USA: CRC Press; 2000. p. 141-143.

[14] ICH, (Q2R1), Harmonized Tripartite Guideline, Validation of analytical procedures: Text and Methodology, IFPMA. Geneva; 2005. p. 1- 13.

[15] ICH, (Q2A), Harmonized Tripartite Guideline, Text on Validation of Analytical Procedures. IFPMA. Geneva; 1994. p. 1-5.

[16] ICH, (Q2B), Harmonized Tripartite Guideline, Validation of Analytical Procedures: Methodology, Text and Methodology, IFPMA. Geneva; 1996. p. 1-8.

[17] The United state Pharmacopoeia, The National formulary, Asian ed. USA: published by United state pharmacopoeial convention; 2003. p. 960.

[18] Nash RA, Wachter AH. Pharmaceutical process validation. 3rd ed. New York: Marcel Dekker Inc.; 2003. p. 1-10.

[19] Gennaro AR. Remington: The Science and Practice of Pharmacy. 20th ed. vol-1. Philadelphia: Lippincott Williams and Wilkin; 2000. Page no.587.

[20] Anjeneyulu Y, Chandrasekhar K, Manikam V. A Textbook of Analytical Chemistry. Pharmamed Press BSP Books; 2008.p.1-2.

[21] Somenath M. Sample Preparation Techniques in Analytical Chemistry. 1st ed. New York: Wiley Interscience; 2003. P.13-16.

[22] Raynord P. Liquid Chromatography for the Analyst. New York: Marcel Dekker Inc; 1994. p.2.

[23] Scott RW. Principal and Practice of Chromatography. 1st ed. Chrom-Ed Book Series. p. 1-3, 12-14.

[24] D. M. Brahmankar and Sunil B. Jaiswal, Biopharmaceutics and Pharmacokinetics, 3rd Edition, Delhi VallabhPrakashan, Page No-9 to 35.

[25] ICH, Guidance on Analytical Method Validation, In: Proceeding of the International Convention on Quality for the Pharmaceutical Industry. Toronto, Canada; 2002.

[26] Alfonso R. Gennaro, Remington: The Science and Practice of Pharmacy, Volume II, 20th Edition, Lippincott Williams and Wilkins Publication.

[27] Pharmaceutical Dosage Forms: Parenteral Medications Volume I, 2nd Edition Edited by Kenneth E. Avis, Herbert A. Liberman and Leon Lachman.

[28] Theory and Practice of commercial Pharmacy, By Leon Lachman, Herbert A. Liberman, Joseph L. Kanig, 3rd Edition, Indian Edition, Varghese publisher, Dadar, Bombay.

[29] The Merck Index, An Encyclopedia Of Chemical, Drug's and Biologicals. Maryadele J. O. Neil. Eds, 14th ed. Whitehouse Station, NJ: Published by Merck lab, Division of Merck and co. Inc; 2006. p. 857, 1422.