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DEVELOPMENT AND VALIDATION OF RP-HPLC METHOD FOR SIMULTANEOUS ESTIMATION OF AMLODIPINE AND VALSARTAN IN ITS BULK AND TABLET DOSAGE FORM BY USING THE QUALITY-BY-DESIGN APPROACH

Shinde Mahesh *, Jondhale Vidhyatai, A. P. Pingale, G. K. Dhikale, D. V. Derle and M. P. Wagh

MVP Samaj's College of Pharmacy, Gangapur road, Nashik - 422002, Maharashtra, India.

Keywords:

Quality by design, Amlodipine, Valsartan, Box-Benhken, Design Space, Process analytical technology

Correspondence to Author:
Shinde Mahesh

MVP Samaj's College of Pharmacy, Gangapur road, Nashik - 422002, Maharashtra, India.

E-mail: Shinde111m@gmail.com

ABSTRACT: This study describes the implementation of a Quality by Design approach to develop and validate the RP-HPLC for amlodipine and valsartan. The reaction surface method optimizes by adopting the three-level Box Behnken design. The three factors selected are methanol and water concentrations (mobile phase), flow rate, and wavelength. The developed chromatographic method was validated against the ICH Q2(R1) guidelines for linearity, range, precision, LOD, and LOQ. The maximum absorbance of amlodipine and valsartan (λ max) was found to be 245 nm. The optimized method consists of mobile phase Methanol: Water (pH 3.0) (80:20), and flow rate 0.9 ml/min, which was optimized by using design expert software. Linearity of the developed method was established over the concentration range of 1 10 µg/ml for Amlodipine and 30 – 200 µg/ml with correlation coefficients (r2) of 0.997 and 0.9993, respectively. The percent RSD for accuracy and precision of the method was found to be less than 2%. The limit of detection (LOD) was 0.08 µg/ml and 0.89 µg/ml for Amlodipine and Valsartan, respectively. The limit of quantitation (LOQ) was 0.02 µg/ml and 2.7 µg/ml for Amlodipine and Valsartan, respectively. They are relatively low to permit the determination of low concentrations of the drug.

INTRODUCTION: The design process is one of the essential variables in the quality of pharmaceutical products. Throughout the product life cycle, the pharmaceutical industry has used the modern concept of Quality by Design (QbD) to apply science-based manufacturing principles to ensure the quality of the formulation and increase efficiencies, provide regulatory relief and flexibility, and offer important business benefits. It encourages the pharmaceutical industry and the FDA to take a more scientific, risk-based, holistic, and proactive approach to drug development.

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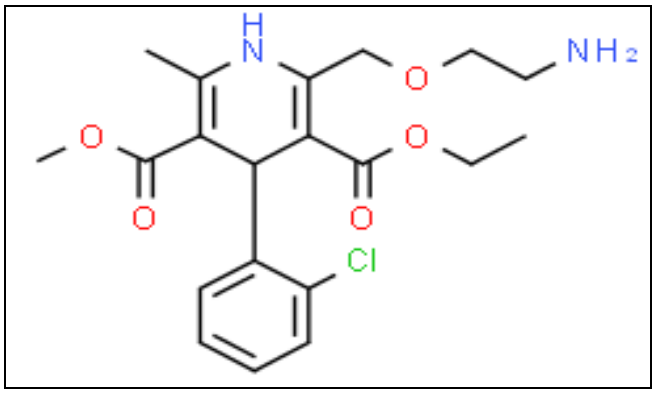
It's also a significant problem for the pharmaceutical business, whose processes are time-bound despite inherent process and material unpredictability. It is crucial to establish the desired product performance profile Target Product Profile (TPP), and Target Product Quality Profile (TPQP), and identify critical quality attributes while designing and developing a product (CQA). On this foundation, we designed the product formulation and process to satisfy the criteria for product attributes such as key material attributes (CMA), critical process parameters (CPP) on the CQAs, and identifying and controlling sources of variability.

High-overall performance liquid chromatography (HPLC) is the maximum flexible and extensively used analytical approach. It uses a liquid cellular segment to split the additives in combination. These additives (or analytes) are first dissolved in a solvent, then pressured to float thru a

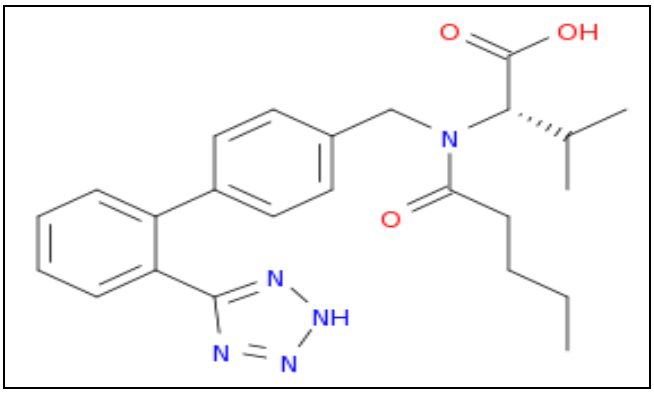
chromatographic column below excessive stress. In the column, the combination is resolved into its additives.

Amlodipine is used to treat high blood pressure (hypertension), some types of angina and other conditions caused by coronary artery disease. Amlodipine is a calcium channel blocker that works by changing the movement of calcium in the heart and blood vessel cells. This widens the blood vessels, increasing blood and oxygen supply to the heart and lowering blood pressure. Amlodipine is considered a peripheral arterial vasodilator that exerts its action directly on vascular smooth muscle to reduce peripheral vascular resistance, causing a decrease in blood pressure. Amlodipine is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the influx of calcium ions into vascular smooth muscle and cardiac muscle.

Valsartan treats high blood pressure (hypertension) in adults and children at least 1 year old. Lowering blood pressure may lower your risk of a stroke or heart attack. Valsartan belongs to a class of drugs called angiotensin II receptor blockers.



STRUCTURE OF AMLODIPINE



STRUCTURE OF VALSARTAN

MATERIALS AND METHODS

Chemicals and Reagents: Pure drug samples of Amlodipine (99%) and Valsartan (99%) were purchased from Macleods Pharmaceutical Ltd, Daman, India. All chemicals such as methanol (HPLC grade), water, ACN (HPLC grade), and O-phosphoric acid (AR grade) were used in experimentation and purchased from the rom Modern science apparatus PVT. Ltd, Nashik.

Instruments: HPLC (WATERS 1525 with binary pumps, UV visible detector; WATERS 2489 with software), UV spectrophotometer (Make: Shimadzu, Model: UV2450 UV probe v 2.3.3), Weighing balance (Make: Shimadzu, Model: AUX220), Ultra-Sonicator (Citizen PVT Ltd), pH meter, FTIR-ATR (Bruker Eco-ATR)

Design Expert® 12.0 Software (Design Expert trial version 12.0; State-Ease Inc., Minneapolis, MN, (USA)

Chromatographic Conditions: HPLC (WATERS 1525 with UV visible detector WATERS 2489). The column Chemsil C18 (250×4.6×5) was used. The optimized mobile phase consists of methanol: water (80:20 v/v) pH 3 with a flow rate of 0.9 ml/min, the run time was 6.2 min, column temperature room temperature, Injection volume 20 µL and detection wavelength 245 nm.

Standard and Stock Solution Preparation: A standard solution of 1000µg/ml of Amlodipine and valsartan was prepared by accurately weighing 10 mg of Amlodipine. Valsartan was transferred into a clean 10 ml volumetric flask, Adding 5 ml of methanol in both volumetric flasks. Sonicate them to dissolve the drug completely, and make up the volume up to 10ml by adding methanol. The solution is used as a standard solution of Amlodipine and Valsartan (1000µg/ml). 0.3 ml of each standard solution was diluted with methanol up to 10 ml in a volumetric flask to get a mixed stock solution of concentration 30µg/ml of amlodipine and valsartan each.

Sample Preparation: Weight an equivalent to 10 mg of the marketed formulation and transfer to a clean 10ml volumetric flask. Added methanol in a volumetric flask and sonicate it to dissolve the tablet in a solvent. Further, make up the volume to

10 ml by using methanol. 0.3 ml of the solution was taken into a clean conical flask, and the volume was made to 10 ml using methanol. The solution was sonicated and filtered through a Whatman filter (0.45µ). This solution was injected into the HPLC.

Mobile Phase Preparation: The pure drug of Amlodipine and Valsartan was spiked into the HPLC system and run in diverse solvent systems. Selection of Proper Column for RP-HPLC method, the various columns are available but our main aim is to resolve the drugs.

On the basis of RP-HPLC mode and the number of carbon present in the molecule, the C18 column of the following configuration was selected for further study.Waters Chemsil C18, 250×4.6mm, 5µ column is used. Selection and Optimization of Mobile Phase, considering sample solubility, stability, and suitability, the different mobile phases and its compositions were tried to obtain a sharp peak.

Different mobile phase compositions containing Methanol and Water in different ratios were tried to select the mobile phase. Finally, the mobile phase composition of Methanol: Water (80:20) pH 3.0 was found to give the best resolution for the drug.

Application of Design of Experiments for Method Optimization: 33 randomized response surface designs with a Box Behnken design were used with 17 trial runs to evaluate the effect of three factors on the three key response variables. In this design, 3 factors were analyzed, each at 3 levels and experimental trials were carried out at all possible combinations. The flow rate, wavelength, and mobile phase composition were selected as independent variables and retention time (RT),

Theoretical Plate number (TPN) and Asymmetric Factor were selected as dependent variables based on risk analysis. The data was processed into Design Expert 12.0 software and analyzed statistically with the help of analysis of variance (ANOVA). The data were also exposed to 3-D response surface methodology to determine the impact of flow rate, pH, and mobile phase composition on dependent variables. The Translation of coded levels in actual values and probable trial runs using 3 Box - Behnken designs are as shown in **Table 1.**

TABLE 1: BOX BEHNKEN FULL FACTORIAL DESIGN

Levels of variables	Concentration of factors		
	Flow rate(ml/min)	Wavelength	Mobile phase composition(methanol: water)
Low level (-1)	0.8	243	70:30
Medium level (0)	0.9	245	80:20
High level (+1)	1	247	90:10

Method Validation: The method was validated for specificity, linearity, precision, accuracy, limit of detection, limit of quantification and stability, as per ICH guidelines Q2 (R2)

System Suitability: System suitability is a Pharmacopeial desideratum and is used to authenticate whether the resolution (here not apply) and reproducibility of chromatographic system are satisfactory for analysis to be done. The tests were performed by collecting data from five replicate injection of standard drug solution 30 ppm). Acceptance Criteria: % Relative standard deviation of the area of analyte peaks in standard chromatograms should not be more than 2.0 %, Theoretical plates of analyte peak in Standard chromatograms should not be less than 2000 and Tailing Factor (Asymmetry) of analyte peaks in Standard Chromatograms should be less than 1.5.

Linearity: Linearity was performed on five levels over 1-10 ppm of amlodipine and 30- 200 ppm. From stock solution aliquots of 0.01, 0.02, 0.03, 0.04, 0.05 ml of Amlodipine and 0.32, 0.64, 0.96, 1.28, 1.6 ml of Valsartan diluted to 10ml with methanol. Each linearity test solution of test concentration prepared in triplicate manner. Linearity was calculated by plotted graph mean area vs concentration. The correlation coefficient was calculated and recorded.

Accuracy: Accuracy was performed over three ranges in triplicate manner i.e., three concentrations and three replicate of each concentration.

Accuracy of the method was established over range of 80, 100 and 120% of working standards.

$$\% \text{ Recovery} = AT / AS \times 100$$

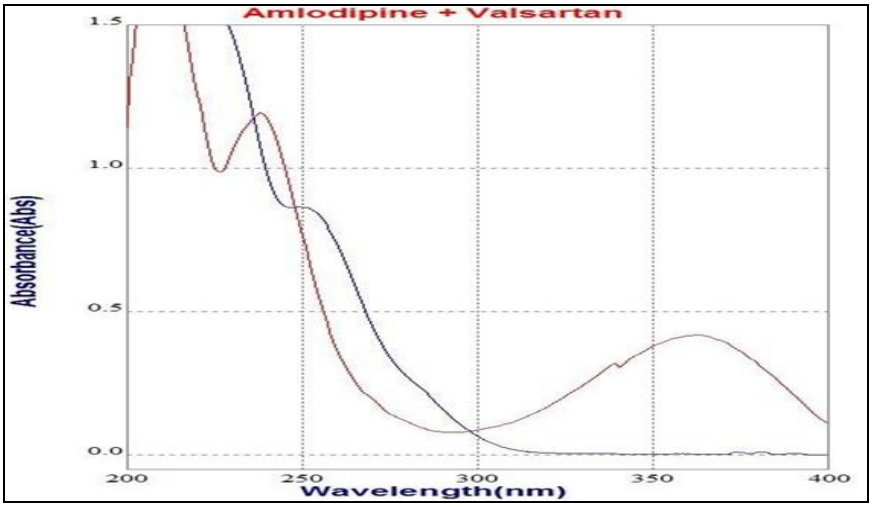
Where AT- peak area of standard amlodipine/ valsartan, AS – peak area of tablet amlodipine/ valsartan.

Precision: Precision was performed by analyzing homogenous sample of amlodipine and valsartan in six times interday or intraday and %RSD was calculated, which should not be more than 2%.

LOD and LOQ: LOD and LOQ were calculated from the Standard deviation of intercept and slope of intercept.

RESULTS AND DISCUSSION:

Selection and Optimization of Wavelength: The HPLC method's sensitivity depends on the on-proper selection of the detected wavelength. An ideal wavelength is responsible for drugs that are to be detected. The λmax of amlodipine and valsartan was observed at 245 nm.



GRAPH 1: ISOSBESTIC WAVELENGTH FOR AMLODIPINE AND VALSARTAN

Method Development: The RP-HPLC method was developed for the simultaneous estimation of amlodipine and valsartan by applying QbD. Range values of parameters were selected by applying the Box Behnken Design of full factorial design. Chemsil C18 (250 × 4.6mm, 5µ) column was used and methanol: water (80:20) was used as the mobile phase, flow rate was maintained 0.9 µL/ml, method was performed at ambient temperature.

After entering the data in Design Expert software, fit summary applied to data after which "quadratic model" was suggested by the software. According to this model following polynomial equation was obtained. Polynomial equation in coded terms,

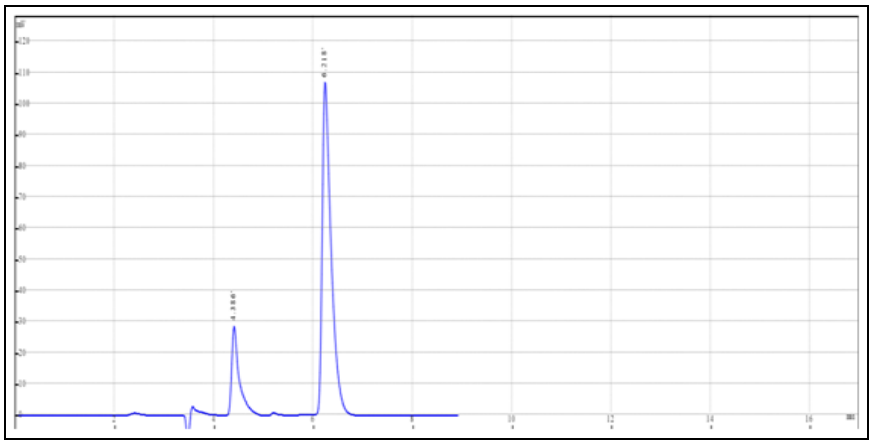
Final Equation in Terms of Coded Factors	
Retention Time =	+6.16 − 1.54 * A − 1.02 * B − 0.0324 * C

The equation in terms of coded factors can be used to make predictions about the response for given levels of each factor. By default, the high levels of the factors are coded as +1 and the low levels are coded as -1. The coded equation is useful for identifying the relative impact of the factors by comparing the factor coefficients.

DOE Optimization Result: The optimization was performed based on response surface modelling using numerical and graphical optimization methods. Desirability is an objective function that ranges from zero outside of the limits to one at the goal. The numerical optimization finds a point that maximizes the desirability function.

The characteristics of a goal may be Chapter 9 Result & Discussion Development and Validation of RP-HPLC method for simultaneous estimation of Amlodipine and Valsartan in its bulk and Tablet dosage form by using Quality by Design Approach altered by adjusting the weight or importance. For several responses and factors, all goals combine into one desirability function. Optimization aims to find a good set of conditions that will meet all the goals.

Trial Methanol: Water (80:20) pH 3.



Name	RT (min)	Area (µV*sec)	USP Tailing	USP Plate Count
Amlodipine	4.3	667467	1.10	7144
Valsartan	6.2	1637042	1.07	7217

Observations: The trial shows good peak shape, USP plate count is acceptable, and retention time is desirable.

Result: Method selected

Optimized Chromatographic Conditions: The following chromatographic conditions were established by trial and error and were kept constant throughout the method.

TABLE 2: OPTIMIZED CHROMATOGRAPHIC CONDITION

Parameter/ conditions	Description/Values
Column name	ChemsilC18, 250 × 4.6mm, 5µ
Detector	245 nm
Flow rate	0.9 µL/ml
Injection volume	20 µL
Column oven Temperature	Ambient Temperature
Retention time	4.3 min and 6.2
Mobile phase	Methanol: Water (80:20) pH 3

TABLE 3: TRANSLATION OF CODED LEVELS IN ACTUAL VALUES

Level of Variables	Concentration of Factors			
	Flow (ml/min)	rate	Wavelength	Mobile Phase Composition(Methanol: Water)
Low level (-1)	0.8		243	70:30
Medium level (0)	0.9		245	80:20
High level (+1)	1		247	90:10

TABLE 4: APPLICATION OF ACTUAL DESIGN OF DOE WITH THE SUBSEQUENT RESPONSE

Run	Factor 1 A: Methanol	Factor 2 B: FlowRate	Factor 3 C: Wavelength	Response 1 Retention Time	Response 2 Retention Time	Response 3 Resolution
1	80	0.8	243	4.85	6.90	4.83
2	70	0.8	245	6.44	9.83	5.15
3	80	0.9	245	4.29	6.11	4.49
4	90	0.9	247	3.82	4.85	2.39
5	80	0.8	247	4.83	6.87	4.82
6	80	0.9	245	4.29	6.11	4.49
7	70	1.0	245	5.28	7.99	5.60
8	70	0.9	243	5.77	8.84	5.05
9	80	0.9	245	4.29	6.11	4.49
10	90	0.9	243	3.82	4.85	2.81
11	80	0.9	245	4.29	6.11	4.49
12	70	0.9	247	5.79	8.85	5.17
13	80	1.0	247	3.95	5.61	5.61
14	90	0.8	245	4.31	5.49	2.79
15	80	1.0	243	3.92	5.57	5.99
16	80	0.9	245	4.29	6.11	4.49
17	90	1.0	245	3.46	4.40	2.76

Accuracy:

TABLE 5: RESULT AND STATISTICAL DATA OF ACCURACY FOR AMLODIPINE

Conc.	Conc.	Area	Mean	SD	% SD	% RSD
1	10	95867				
	10ss	96933	96197	638.5264286	0.66376959	
	10	95791				
	30	145875				
2	30	143218	144399.6667	1352.62424	0.93672255	
	30	144106				0.173992027
	50	194646				
3	50	195575	195749.6667	1200.567505	0.61331778	
	50	197028				

TABLE 6: RESULT AND STATISTICAL DATA OF ACCURACY FOR VALSARTAN

Conc.	Conc.	Area	Mean	SD	% SD	% RSD
1	10	2625272				
	10	2614243	2626372	12714.73716	0.48411791	
	10	2639601				
	30	5470416				
2	30	5469573	5494281.333	42068.14094	0.7656714	
	30	5542855				0.165086452
	50	8606268				
3	50	8683378	8636651.333	41070.87086	0.47554161	
	50	8620308				

Precision

TABLE 7: INTRADAY PRECISION FOR AMLODIPINE AND VALSARTAN

Sr. no.	Area for Amlodipine	Area for Valsartan
1	145875	5470416
2	143218	5469573
3	144106	5542855
4	143605	5483103
5	145459	5459442
6	146364	5399900
Mean	144771.2	5470882
% RSD	0.90%	0.84%

TABLE 8: INTERDAY PRECISION FOR AMLODIPINE AND VALSARTAN

Sr. no.	Area for Amlodipine	Area for Valsartan
1	145875	5470416
2	143218	5469573
3	144106	5542855
4	142840	5472721
5	143274	5454889
6	143542	5448667
Mean	143218.7	5458759
% RSD	0.76%	0.62%

TABLE 9: ANALYTICAL DATA FOR CHANGE IN PH OF AMLODIPINE AND VALSARTAN

Sr. no.	Area for Amlodipine	Area for Valsartan
1	121954	3987675
2	122212	4023352
3	121068	4014905
Mean	121745	4008644
SD	600.041	18644.4
% SD	0.4928685	0.46510392

TABLE 10: ANALYTICAL DATA FOR CHANGE IN WAVELENGTH OF AMLODIPINE AND VALSARTAN

Sr. no.	Area for Amlodipine	Area for Valsartan
1	121431	4034427
2	121068	4014905
3	122731	4065154
Mean	121743	4038162
SD	874.389	25331.9
% SD	0.71822341	0.62731165

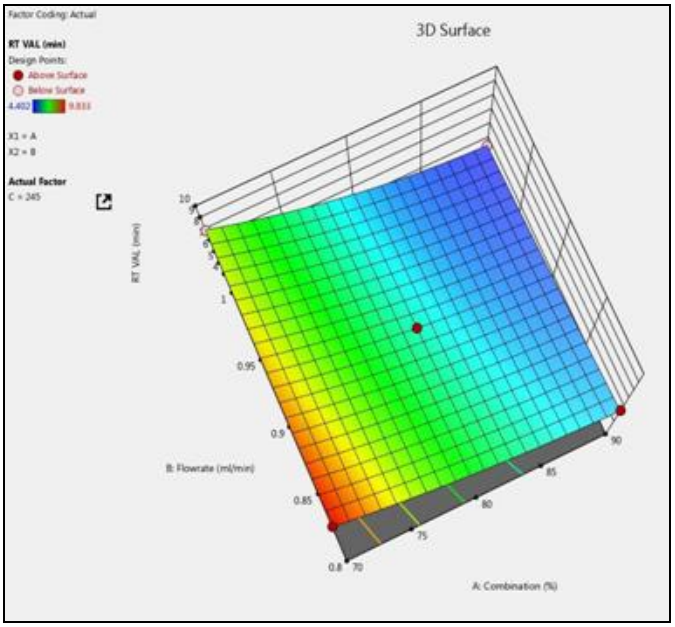


FIG. 1: 3D RESPONSE PLOT OF RETENTION TIME AGAINST FLOW RATE AND COMBINATION FOR AMLODIPINE

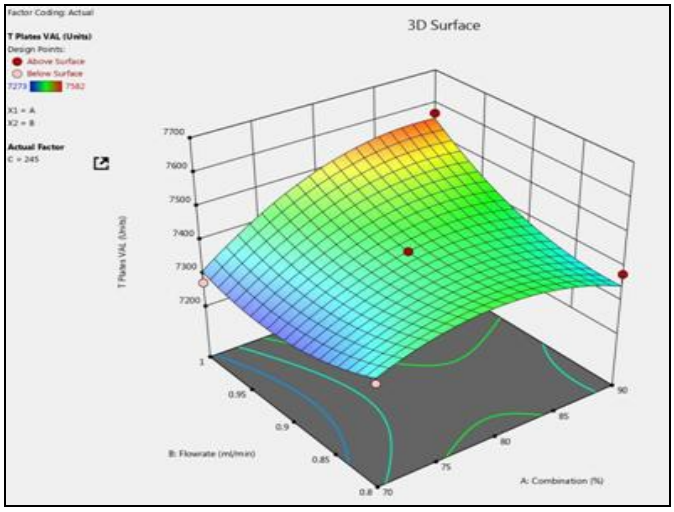


FIG. 2: 3D RESPONSE PLOT OF RETENTION TIME AGAINST FLOW RATE AND COMBINATION FOR VALSARTAN

CONCLUSION: RP-HPLC binary isocratic system was used for the analysis. Chesil C18 (250mm x 4.6 ID, Particle size: 5 microns was used as a stationary phase. The solution of Amlodipine and Valsartan in appropriate dilution was scanned using UV visible spectrophotometer in the spectrum mode between the wavelength range of 400 nm to 200 nm. The drug shows maximum absorbance at 245 nm (λ Max).

The quality by Design approach has been successfully used to develop the RP-HPLC Method for estimating Amlodipine and Valsartan. The developed method employed mobile phase Methanol: Water (80:20) (pH 3.0) pH adjusted by o-phosphoric acid, and flow rate 0.9 ml/min, which was optimized with the help of design expert software. Before method optimization, screening studies were carried out on different mobile phases of varying compositions. Based on the results obtained from these studies, a suitable mobile phase with appropriate composition was selected and utilized for method development using the QbD methodology. A systematic approach was utilized to develop an efficient and robust method, which begins with determining target profile characteristics, risk assessment, design of experiment, and validation. The study was done by using 33 Box Behnken response surface designs. In this study interaction of 3 factors, Flow Rate, Wavelength, and Mobile Phase Composition, vary at 3 levels. The effect of such critical process parameters on the critical quality attribute of the method is studied. Responses in terms of retention times and resolution were evaluated throughout all the runs in design. Method Operable Design Region (MODR), also termed Analytical Design Space (ADS), was developed by taking such runs. A desirability function was applied to determine the optimum conditions. Optimum conditions were obtained; the one with higher desirability was selected. Replicates of the run having optimized conditions were taken to confirm the predicted response with the actual response. The RP-HPLC method developed for estimating Amlodipine and Valsartan was validated concerning ICH Q2 (R1) guideline. Linearity of the developed method was confirmed over the concentration range of 10 - 60 µg/mL for Amlodipine and Valsartan with correlation coefficients of 0.9997 and 0.9993, respectively.

The percentage RSD for the method's precision and accuracy was less than 2%. The system suitability test ensures that the analytical system works properly and gives accurate and precise results. System suitability tests include tailing factor, number of theoretical plates, area, *etc*. The results of all system suitability parameters were acceptable in their limits defined by official guidelines. The proposed high-performance liquid chromatographic method has also been evaluated for accuracy and precision and proved to be convenient and effective for the quality control of Amlodipine and Valsartan. Moreover, the lower solvent consumption and the short analytical run time of 8.91 min lead to a cost-effective and environmentally friendly chromatographic procedure. Thus, the proposed methodology is rapid, and selective, requires a simple sample preparation procedure, and represents a good procedure for Amlodipine and Valsartan.

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CONFLICTS OF INTEREST: Nil

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