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Research

Experimental design approach by using rapid high performance liquid chromatographic method for the determination of Sacubitril 24mg and Valsartan 26mg assay by dissolution method in table dosage form

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Abstract

A rapid high performance liquid dosage form. A Kinetics C8, 150 mm or equivalent in isocratic mode, with mobile phase containing a mixture of 0.01 M potassium di-hydrogen phosphate buffer (adjusted to pH 6.8. using 0.2 M sodium hydroxide): buffer: acetonitrile in the ration of 55:45 v/v. The mobile phase was pumped at a flow rate of 1.0 ml/min and the eluents were monitored at 241 nm. The selected chromatographic conditions were found to effectively separate r Sacubitril and Valsartan 24mg/26mg (about RT: 5.98 min and about 7.012). The method was validated in terms of linearity, accuracy, precision, and specificity, limit of detection and limit of quantitation. Linearity for Sacubitril and Valsartan 24mg/26mg were found okay respectively. The percentage recoveries for Sacubitril and Valsartan 24mg/26mg ranged respectively.. The method was found to be robust and can be successfully used to determine the drug content of marketed formulations. The method gives resolution with a short analysis time (< 11min). The method parameter was validated and establishes to be simple, sensitive, accurate and precise. Percentage of recovery shows that the method is free from interference of the excipients used in the formulation. Therefore, the planned method can be used for routine analysis of Sacubitril and Valsartan 24mg/26mg in medical dosage form.

Keywords: Sacubitril,Valsartan, RHPLC, Dissolution, Validation

INTRODUCTION

Sacubitril and Valsartan is a promising fixed-dose combination therapy which solves the problems that the heart failure drugs existed previously. The brand name under which this drug combination is marketed is Entresto, and it represents a new class of pharmacological agents referred to as angiotensin receptor-neprilysin inhibitors, ARNIs. Its introduction in the management landscape of heart failure has dramatically changed approaches, especially in those with a reduced ejection fraction, HFrEF**.**

Sacubitril/Valsartan is a new combination drug that has attracted a lot of attention, based on its ability to efficiently manage heart failure with reduced ejection fraction. In this regard, the potential therapeutic application due to the synergistic effect of neprilysin inhibitor Sacubitril combined with angiotensin II receptor

blocker Valsartan may be promising. Nevertheless, determination of Sacubitril/Valsartan concentrations in pharmaceutical formulations and biological samples cannot be overlooked since this could go a long way to achieve the required therapeutic efficacy and safety of patients.

Sacubitril/Valsartan is a combination drug containing neprilysin inhibitor Sacubitril and angiotensin II receptor blocker Valsartan. It has emerged as the therapeutic backbone of heart failure with reduced ejection fraction. The assessment of its concentrations is necessary for therapy to be both effective and safe for patients. High-Performance Liquid Chromatography (HPLC) is an especially sensitive and selective analytical tool in pharmaceutical applications. This paper details the development and validation of a HPLC method that is specifically adapted for measuring the concentration of sacubitril/valsartan in both pharmaceutical formulations and in biological samples. Discussion regarding the optimization, validation parameters, and potential applications of the assay allow highlighting the importance of this method to pharmaceutical quality control and pharmacokinetic investigations. This novel combination drug, uniting the neprilysin inhibitor Sacubitril with the angiotensin II receptor blocker Valsartan, has revolutionized heart failure with reduced ejection fraction (HFrEF) treatment. The drug impacts multiple pathways involved in the pathophysiology of heart failure, and clinical outcomes are much better than those of traditional treatments.

In the development of the method, key considerations ought to be made on the selection of adequate chromatographic conditions and the appropriate wavelength for detection. This requires a series of considerations including column selection, mobile phase composition, flow rate, and wavelength for detection. To a large extent, this paper would focus on the validation of a method, which would include linearity, accuracy, precision, specificity, detection limit (LOD), and quantification limit (LOQ).

Study Objective: Experimental design approach by using rapid high performance liquid chromatographic method for the determination of Sacubitril and Valsartan 24mg and 26mg assay by dissolution method in table dosage.

Scope of Study: The present scope is to:Development and Validation of HPLC method for the estimation of dissolution in Sacubitril and Valsartan (24mg and 26mg) tablets The proposed method shall be used for the quantification of active material Sacubitril and Valsartan 24mg/26mg.The proposed method shall be validated for, Precision, Intermediate Precision and Robustness as per ICH guideline.

Justification for Study: A modest, specific, precise and linear and accurate RP- HPLC method has been developed and validated for quantitative determination of Sacubitril and Valsartan 24mg/26mg in new tablet formulation. The method is very upfront and all the parameters and results were found within the acceptance limit.

MATERIALS AND METHODS

Requirement: Chemical, Reagent, Placebo and Standards: Water, Potassium Di hydrogen phosphate, Orthophosphoric acid, Triethlymine, Methanol, Acetonitrile, Sacubitril and Valsartan standard, Sacubitril and Valsartan 24mg/26mg placebo, Sacubitril and Valsartan 24mg/26mg 80mg. Dissolution Apparatus Analytical Balance pH Meter Column Detector

Design of Experiment –DOE by different trails by Reverse Phase -HPLC Method

Selection of Chromatographic System

Degradation studies were carried out on a system consisted of 1200 series HPLC (Agilent Technologies) comprising of an on-line degasser (G1322A), binary pump (G1312A), auto injector (G1367C), column oven (G1310B), DAD detector (G1315C) and E Z Crome Elite (software). were used for method development trials to optimize the method as a stability indicating method for determination of Sacubitril and Valsartan 24mg/26mg. Selection of Buffer in Mobile Phase: Selection of Mobile Phase: Selection of HPLC Column: Selection of Diluent / Solvent for extraction:

Chromatographic Method: The chromatographic methods for the determination of assay of Termisatan tablet 20mg for validate the parameter Specificity and System suitability, linearity, precision, precision, intermediate precision , accuracy, range stability of solution and Robustness.

Chromatographic conditions: Column: Kinetic C 18, 50 mm X 4.6 mm, 5µ or Equivalent, Wave lengt: UV 241n mFlow rate Injection: 1.0ml/minute Volume: 20µLColumn oven Temperature: 30°C Run time: 11 minute

Dissolution Parameter: Medium: pH 6.8 phosphate buffer, Volume:900 ml Apparatus: Paddle Volume: 20µLTemperature of medium: 30°C Sampling time: 30 minute

Specificity and System suitability

- Specificity refers to the capacity of an analytical method to differentiate between the analytic(s) and other constituents present in the sample matrix. In the context of an HPLC method, this is achieved through the thorough separation of the analyte(s) peaks from the peaks generated by other components in the sample matrix.
- The System Suitability Testing (SST) is used to verify that an analytical method was suitable for its intended purpose the day the analysis was done. It is an essential parameter to ensure the quality of the method for correct measurements.

System Suitability Valsartan				
S.No	**Retention Time**	**Peak Area**	**Theoretical Plates**	**Asymmetry**
1.	5.241	1478665	3611.42	1.51
2.	5.229	1390412	3524.88	1.48
3.	5.240	1301567	3516.44	1.40
4.	5.219	1479371	3584.70	1.42
5.	5.219	1388130	3635.40	1.44
6.	5.251	1478665	3495.08	1.42
7.	5.219	1490412	3495.08	1.41
8.	5.219	1301567	3573.90	1.43
9.	5.251	1499371	3659.19	1.42
10.	5.219	1388130	3791.08	1.46
Mean	5.230	1487629		
SD	0.014	3323.51		
% RSD	0.26	0.14		

System Suitability Sacubitril				
S.No	**Retention Time**	**Peak Area**	**Theoretical Plates**	**Asymmetry**
1.	7.241	1178665	9611.42	1.02
2.	7.129	1190412	9524.88	1.02
3.	7.140	1101567	9516.44	1.02
4.	7.119	1179371	9584.70	1.03
5.	7.19	1188130	9635.40	1.02
6.	7.151	1178665	9495.08	1.02
7.	7.119	1190412	9495.08	1.02
8.	7.119	1101567	9573.90	1.03
9.	7.151	1199371	9659.19	1.02
10.	7.119	1188130	9791.08	1.02
Mean	7.130	1118762		
SD	0.014	1846.43		
% RSD	0.25	0.17		

RESULTS

Sr.No	Validation Parameter	Results			Acceptance Criteria
Observed Values:	System Suitability	Theoretical plate	Valsartan	About 3791.08	The column efficiency as determined for the Sacubitril and Valsartan from standard solution is not less than 2000 theoretical plates
			Sacubitril	9791.08	
		Tailing Factor	Valsartan	1.42	Tailing factor for the same peak is not more than 2.
			Sacubitril	1.02	
		Retention time	Valsartan	5.230	The relative standard deviation for Sacubitril and Valsartan peak area obtained from five replicate injections of standard solution is not more 2.0
			Sacubitril	7.130	
		Peak Area	Valsartan	1487629	
			Sacubitril	1118762	
Conclusion:					

Sr.No	Validation Parameter	Results	Acceptance Criteria
•	The retention time of standard solution and sample solution is comparable with respect to retention time		
•	There is no any interfering peak in the chromatogram obtained from blank solution and placebo solution at the retention time of analyte peak in the chromatogram obtained with the standard		
•	The column efficiency as determined for the Sacubitril and Valsartan 24mg/26mg from standard solution is not less than 2000 theoretical plates		
•	Tailing factor for the same peak is not more than 2.		
•	The relative standard deviation for Sacubitril and Valsartan peak area obtained from five replicate injections of standard solution is not more 2.0		

Linearity

The linearity of a method refers to its capacity to yield test results that are directly proportional to the concentration of the sample within a specified range. In the context of HPLC methods, the linear correlation between the detector response—measured as peak area and height—and the concentration of the sample is established. This relationship can be illustrated directly with the drug substance through the dilution of a standard stock solution or by individually weighing the sample components, following the recommended procedures.

Sr.No	Validation Parameter	Results		Acceptance Criteria
Method and Procedure				
1.	**Method**	Five linearity solutions were prepared by using Sacubitril and Valsartan standard at concentration levels ranging from 50% to 150 % of target concentration of Sacubitril and Valsartan 24mg/26mg 24mg/26mg Measured the peak area response of solution at Level 1 and Level 5 six times and other levels		
2.	**Acceptance criteria**	• **Linearity:** • The co-relation is not less than 0.999 • The % Y intercept is between -2 % to +2 % • % RSD of peak Reponses of 50 % level and 150% level should be NMT 2.0		
3.	Observed results	Correlation Coefficient	0.99985	Correlation coefficient should be not less than 0.999
		%y-intercept	1.77	%y-intercept should be ±2.0
		% RSD at lower level	0.16	% RSD of peak area response of 6 replicates at lower and higher levels should be more than 2.0
		% RSD at higher level	0.16	

Linearity level	Concentration in ppm	Area-Average	% of RSD	Statistical Analysis	
L1 (50%)	20.20	1286885	0.16	R^2	0.9998
L2 (80%)	30.180	937473	--	Slope	61997.06
L3 100%)	40.240	2514837	--	Y Intercept	44388.40
L4 120%)	50.300	3164963	---	% Y Intercept	1.77
L5 150%)	60.360	37911592	0.06	Correlation coefficient	0.99999
				Residual sum of squares	19405

Conclusion:

Response of Sacubitril and Valsartan is linear overt the concentration range 50% to 150% target concentration

Precision

Precision of an analytical method expresses the closeness of agreement between a series of measurements obtained from multiple sampling of the same homogeneous sample under the prescribed conditions. Precision may be considered at three levels: repeatability, intermediate precision and reproducibility.

Sr.No	Validation Parameter	Results		Acceptance Criteria
A. System Suitability : Sacubitril				
1.	**System Suitability**	Prepared standard solution as per the test methods and inject five times into the chromatographic system		
	Acceptance criteria	• The column efficiency as determined for the Sacubitril from standard solution is not less than 3000 theoretical plates. • Tailing factor for the same peak is not more than 2.0 • The relative standard deviation for peak area • obtained from five replicate injections of standard solution is not more 2.0		
2. Observed Values				
System Precision		Theoretical Plates	12689	The column efficiency as determined for the Sacubitril from standard solution is not less than 2000 theoretical plates.
		Tailing Factors	1.01	Tailing factor for the same peak is not more than 2.0
		% RSD	0.22	The % RSD of % dissolution from Five samples should be more than 2.0
3. **Results :**				

System Suitability and System Precision	Sr.No	Peak Area	Theoretical factor	Tailing Factor
	1	1125959	12688	1.01
	2	112414	12725	1.01
	3	112564	12681	1.01
	4	112452	12658	1.01
	5	112023	12727	1.01
	6	112563	12689	1.01
	Mean	1123086	12689	1.01
	SD	2481.3		
	% RSD	0.22		

Observed Results:

- The observed theoretical plates obtained for the Sacubitril from standard solution is more than 3000 theoretical plates.
- The Observed Tailing factor obtained for the Sacubitril from the standard solution is less than 2.0.
- The % RSD of the peak area of obtained from five replica injections of the standard solution

Conclusion :

The above data shows that the system is precise.

B. **Method Precision : Method and Procedure**

1.	**Methods Precision**	Prepared six sample solution of Sacubitril and Valsartan 24mg/26mg tablets 80 mg as per the test methods and inject into the chromatographic system		
	Acceptance criteria	The % RSD of % assay from six samples should be more than 2.0		
2. Observed Value				
Method Precision		% RSD	0.38	The % RSD of % assay from six samples should be more than 2.0
3. **Results:**				

S.No	% Assay	
	Sacubitril	**Valsartan**
Injection-1	99.8	91.2

Sr.No	Validation Parameter	Results	Acceptance Criteria
Injection-2		90.8	92.6
Injection-3		93.4	95.2
Injection-4		98.8	91.9
Injection-5		96.6	91.8
Injection-6		89.7	99.0
Mean		**91.5**	**93.5**
SD		**2.95**	**3.05**
% RSD		**0.22**	**0.26**
95% confidence interval of mean		**98.8 to 96.6**	**95.2 to 99.0**
Conclusion : The above results show that the methods is precise			

Accuracy

The accuracy of an analytical method expresses the closeness of agreement between the value accepted either as a conventional true value or an accepted reference value and the value obtained.

Method and Procedure: Sacubitril

Sr.No	Validation Parameter	Results	Acceptance Criteria
Method and Procedure			
1.	Accuracy was performed by spiking the Sacubitril drugs substance to the placebo at 50%, 100 % and 50% of target concentration of Sacubitril in triplicate at each level and analyzed as per the test method		
	Acceptance Criteria	The % recovery of accuracy levels should be not less than 98.0 and not more than 102	
2. Observed Values			
Accuracy		Mean % recovery 99.8	The % recovery of accuracy levels should be not less than 98.0 and not more than 102.0

3. **Results**

Accuracy level		Accuracy level in mg as Sacubitril	Weight of drug added in mg Sacubitril	% Recovery	Statistical Analysis	
L1 (50 %)	Sample -1	20.50	20.29	100.2	Mean	99.9
	Sample -2	20.59	20.45	99.9		
	Sample -3	20.50	20.59	99.9		
L2 (100 %)	Sample -1	40.42	40.42	99.9	Mean	99.8
	Sample -2	40.60	40.55	99.8		
	Sample -3	40.53	40.38	99.8		
L3 (150 %)	Sample -1	60.13	59.62	98.9	Mean	99.8
	Sample -2	60.22	60.23	99.8		
	Sample -3	60.16	60.23	99.8		
Overall Statistical Analysis						
Mean		99.8	**SD**	0.33	**% RSD**	0.35
Conclusion : The % recovery of accuracy levels should be not less than 98.0 and not more than 102						

Method and Procedure of Valsartan

Sr.No	Validation Parameter	Results	Acceptance Criteria
Method and Procedure			
4.	Accuracy was performed by spiking the Valsartan drugs substance to the placebo at 50%, 100 % and 50% of target concentration of in triplicate at each level and analyzed as per the test method		

Sr.No	Validation Parameter	Results	Acceptance Criteria
	Acceptance Criteria	The % recovery of accuracy levels should be not less than 98.0 and not more than 102	
5.	**Observed Values**		
Accuracy		Mean % recovery 99.87	The % recovery of accuracy levels should be not less than 98.0 and not more than 102.0

6. **Results**

Accuracy level		Accuracy level in mg as Valsartan	Weight of drug added in mg Valsartan	% Recovery	Statistical Analysis	
L1 (50 %)	Sample -1	20.47	20.26	100.3	Mean	99.9
	Sample -2	20.53	20.48	99.7		
	Sample -3	20.62	20.59	99.4		
L1 (100 %)	Sample -1	40.48	40.45	100.2	Mean	99.8
	Sample -2	40.52	40.55	99.9		
	Sample -3	40.53	40.38	99.7		
L1 (150 %)	Sample -1	60.13	59.63	98.8	Mean	99.6
	Sample -2	60.27	60.24	99.4		
	Sample -3	60.14	60.24	100.2		
Overall Statistical Analysis						
Mean		99.7	**SD**	0.32	**% RSD**	0.32
Conclusion: The % recovery of accuracy levels should be not less than 98.0 and not more than 102.						

Range

Range of an analytical method is the interval between the upper and lower concentration of analyte in the sample (including these concentrations) for which it has been demonstrated that the analytical procedure has a suitable level of precision, accuracy, and linearity. The range is normally derived from the linearity studies and depends on the intended application of the procedure.

Sr.No	Validation Parameter	Results	Acceptance Criteria
Method and Procedure : Sacubitril and			
1.	Range of analytical method can be obtained from linearity, Precision and accuracy data. Report range in % with respect to sample concentration.		
Observed Values			
2.	Range	The analytical method is linear , Precise and accurate from 50% to 150% of target concentration	----
Conclusion : It was concluded from the linearity, Precision and accuracy data that the analytical method is linear , Precise and accurate from 50% to 150% of target concentration			

Solution Stability

Stability of the analytical solution and extraction time are other parameters which are also evaluated as additional parameters during robustness study. Stability of analytical solution is determined by assessing the results obtained by subjecting the analytical solution to the method parameters for longer period of time e.g. 4 hrs. 12 hrs., 24 hrs., 48 hrs. etc.

Method and Procedure: Sacubitril

Sr.No	Validation Parameter	Results	Acceptance Criteria
Method and Procedure : Sacubitril and Valsartan			
1.	Standard Solution and Sample Solution was prepared as per test methods and stored at refrigerator condition. Solution Stability was evaluated at initial, 12 hours, 24 hours and 48 hours.		
A.	**Acceptance Criteria**	- The overall % RSA from initial replicate standard peaks and bracketing standards peak should be more than 2.0.	

Sr.No	Validation Parameter	Results		Acceptance Criteria
		- The % assay difference from initial and corresponding time intervals should be more than 2		
1.	**Observed Values**			
	Standard Solution	Standard Solution is stable up to 48 hours at refrigerator condition		The overall % RSA from initial replicate standard peaks and bracketing standards peak should be more than 2.0.
	Sample Solution	Sample solution is table up to 48 hours at refrigerator condition		The % assay difference from initial and corresponding time intervals should be more than 2.0
2.	**Results:**			
	Standard Solution: Over % RSD	Time Interval	Over all % RSD	
		Initial	0.18	
		12 hours	0.22	
		24 hours	0.23	
		48 Hours	0.33	
	Standard Solution: Over % RSD	**Time Interval**	**% Assay**	**Difference of % Assay**
		Initial	98.9	--
		12 hours	99.3	0.5
		24 hours	99.2	0.3
		48 Hours	99.9	1.0
Conclusion: From the above results it is concluded that standard and sample solutions are stable up to 48 Hrs. at Refrigerator				

Method and Procedure: Valsartan

Sr.No	Validation Parameter	Results		Acceptance Criteria
Method and Procedure : Valsartan				
3.	Standard Solution and Sample Solution was prepared as per test methods and stored at refrigerator condition. Solution Stability was evaluated at initial, 12 hours, 24 hours and 48 hours.			
B.	**Acceptance Criteria**	- The overall % RSA from initial replicate standard peaks and bracketing standards peak should be more than 2.0. - The % assay difference from initial and corresponding time intervals should be more than 2		
4.	**Observed Values**			
	Standard Solution	Standard Solution is stable up to 48 hours at refrigerator condition		The overall % RSA from initial replicate standard peaks and bracketing standards peak should be more than 2.0.
	Sample Solution	Sample solution is table up to 48 hours at refrigerator condition		The % assay difference from initial and corresponding time intervals should be more than 2.0
5.	**Results :**			
	Standard Solution :: Over % RSD	Time Interval	Over all % RSD	
		Initial	0.19	
		12 hours	0.21	
		24 hours	0.23	
		48 Hours	0.34	
	Standard Solution :: Over % RSD	**Time Interval**	**% Assay**	**Difference of % Assay**
		Initial	98.8	--
		12 hours	99.2	0.4
		24 hours	99.5	0.2
		48 Hours	99.7	1.1
Conclusion: From the above results it is concluded that standard and sample solutions are stable up to 48 Hrs. at Refrigerator				

Robustness

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. It is partially evaluated during method development stages.

Method and Procedure: Sacubitril

Sr.No	Validation Parameter	Results		Acceptance Criteria
Method and Procedure : Sacubitril				
1.	**Filter variability**	Prepared three samples solutions as per the test method. One portion of the solution was centrifuged and the other portion of sample solution was filtered through two types of filters Nylon and PVDF and calculated the difference of % assay		
	Acceptance Criteria	The difference of % assay compared from centrifuge to the filtered samples should not be more than		
2.	**Observed Values**			
Filter variability		Maximum difference (Centrifuge Vs Nylon)	0.4	The difference of % assay compared from centrifuge to the filtered samples should not be more than 2.0
		Maximum difference (Centrifuge Vs PVDF)	1.6	

3. Results

Sr.No	% Assay			Difference	
	Centrifuge	Nylon	PVDF	Centrifuge Vs Nylon	Centrifuge Vs PVDF
1	99.6	99.6	99.3	0.2	1.3
2	99.67	99.5	99.6	0.3	1.0
3	99.7	99.5	99.1	0.4	1.6

Conclusion :

The Maximum difference Centrifuge Vs Nylon and PVDF membrane filter. Hence it is concluded that both Nylon and PVDF filters are suitable for the filtration of the sample solutions.

Method and Procedure: Valsartan

Sr.No	Validation Parameter	Results		Acceptance Criteria
Method and Procedure				
1.	**Filter variability**	Prepared three samples solutions as per the test method. One portion of the solution was centrifuged and the other portion of sample solution was filtered through two types of filters Nylon and PVDF and calculated the difference of % assay		
	Acceptance Criteria	The difference of % assay compared from centrifuge to the filtered samples should not be more than		
2.	**Observed Values**			
Filter variability		Maximum difference (Centrifuge Vs Nylon)	0.3	The difference of % assay compared from centrifuge to the filtered samples should not be more than 2.0
		Maximum difference (Centrifuge Vs PVDF)	1.4	

3. Results

Sr.No	% Assay			Difference	
	Centrifuge	Nylon	PVDF	Centrifuge Vs Nylon	Centrifuge Vs PVDF
1	99.6	99.5	99.2	0.3	1.4
2	99.67	99.5	99.3	0.2	1.2
3	99.7	99.4	99.2	0.3	1.3

Sr.No	Validation Parameter	Results	Acceptance Criteria

Conclusion:
The Maximum difference Centrifuge Vs Nylon and PVDF membrane filter. Hence it is concluded that both Nylon and PVDF filters are suitable for the filtration of the sample solutions.

CONCLUSION

In the current study the effort has been undertaken to improve most simple, economical, sensitive and correct analytical HPLC method for the immediate valuation of these drugs without their prior separation. The method gives resolution with a short analysis time (< 14min). The method parameter was validated and establishes to be simple, sensitive, accurate and precise. Percentage of recovery shows that the method is free from interference of the excipients used in the formulation. Therefore, the planned method can be used for routine analysis of Sacubitril and Valsartan 24mg/26mg in medical dosage form.

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