

## DEVELOPMENT AND VALIDATION OF STABILITY INDICATING CHROMATOGRAPHIC METHOD FOR SIMULTANEOUS ESTIMATION OF SACUBITRIL AND VALSARTAN IN PHARMACEUTICAL DOSAGE FORM

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### ABSTRACT

**Objective:** This study aims to develop and validate a stability indicating HPLC method for simultaneous estimation of sacubitril and valsartan in pharmaceutical dosage form.

**Methods:** Sacubitril and valsartan separation were achieved by LC-20 AT C<sub>18</sub> (250 mm x 4.6 mm) column and buffer (potassium phosphate, pH 3.0): methanol (50:50) as mobile phase, at a flow rate of 1 ml/min (millilitre per minute). Detection was carried out at 224 nm (nanometer). The different HPLC experimental parameters were optimized and the method was validated according to the standard guideline. Forced degradation experiments were carried out by exposing sacubitril and valsartan standard and sample for thermal, photolytic, oxidative and acid-base hydrolytic stress conditions.

**Results:** Retention time of sacubitril and valsartan were found to be 4.170 min (minute) and 6.530 min (minute) respectively. The method has been validated for linearity, accuracy, precision, LOD, and LOQ. Linearity observed for sacubitril is 12.25-36.75 µg/ml (microgram per milliliter) and for valsartan is 12.75-38.25 µg/ml (microgram per milliliter). The results showed that sacubitril and valsartan and the other degradation products were fully resolved and thus the proposed method is stability-indicating.

**Conclusion:** The proposed HPLC method was found to be simple, specific, precise, accurate, rapid and economical for simultaneous estimation of valsartan and sacubitril in bulk and tablet dosage form. Thus the validated economical method was applied for forced degradation study of sacubitril and valsartan tablet.

**Keywords:** Sacubitril, Valsartan, RP-HPLC, Stability indicating RP-HPLC method, Validation

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### INTRODUCTION

Sacubitril is chemically 4-[[[(2S, 4R)-5-ethoxy-4-methyl-5-oxo-1-(4-phenyl-phenyl) pentan-2-yl] amino]-4-oxobutanoic acid [1]. Sacubitril is an antihypertensive drug used in combination with valsartan for the treatment of heart failure. [2-3]. Valsartan is a nonpeptide, orally active and specific angiotensin II receptor blocker acting on the AT1 receptor subtype. Valsartan is chemically N-(1-oxopentyl)-N-[[2'-(1Htetrazol-5-yl)[1,1'-biphenyl]-4-yl]methyl]-L-valine [4-7]. Methods such as HPLC [8-10], LC-MS [11-12], protein precipitation [13] and

simultaneous UV-spectrophotometric methods [14-15] are reported for estimation of valsartan alone or in combination with other agents. A literature search reveals that only two analytical methods were reported for simultaneous estimation of sacubitril and valsartan from rat plasma using LC-MS/MS [16] and from a synthetic mixture using HPLC [17]. There is no stability indicating analytical methods were reported for simultaneous estimation of sacubitril and valsartan. Hence a simple, rapid, sensitive and accurate stability indicating HPLC method was developed for the simultaneous estimation of sacubitril and valsartan from API and pharmaceutical dosage form.

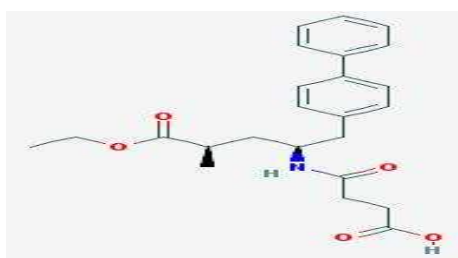


Fig. 1: Sacubitril structure from pub chem

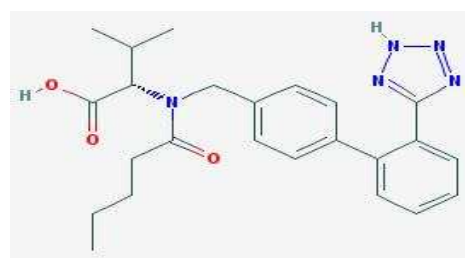


Fig. 2: Valsartan structure from pub chem

### MATERIALS AND METHODS [17]

#### Materials and reagents

Acetonitrile, potassium di-hydrogen phosphate, orthophosphoric acid and methanol of HPLC and AR grade were procured from Merck and Rankem lab ltd. Sacubitril and valsartan standards were received as gift samples from Yash Pharma and RPG Life Science, Ahmedabad, India, respectively.

#### Equipment

Chromatographic separation was performed on HPLC system consist of model Shimadzu LC-20 AT having a SPD-20AT detector and rheodyne injector with 20µl loop volume. Spinchrom software was applied for data collecting and processing. UV spectrophotometer which consists of model Systronic 119 is also used to measure the wavelength of the solution of Sacubitril and Valsartan.

### Preparation of standard stock solution

Accurately weighed quantity of 24.5 mg (milligram) sacubitril and 25.5 mg (milligram) valsartan API were transferred into 100 ml (milliliter) volumetric flask and dissolved in HPLC grade methanol using ultra sonication and diluted up to mark to give a stock solution having concentration of 245 µg/ml sacubitril and 255 µg/ml valsartan.

### Preparation of working standard solution

From above standard stock solution of sacubitril and valsartan, 1 ml of solution was taken into 10 ml volumetric flask and was made to the mark with the mobile phase to get 24.5 µg/ml of sacubitril and 25.5 µg/ml of valsartan.

### Preparation of sample stock solution

The average weight of 10 tablets was determined and was ground in

a mortar. Sample stock solution was prepared by dissolving tablet powder equivalent to 24.5 mg of sacubitril or 25.5 mg of valsartan was transferred to 100 ml volumetric flask. Then 60 ml methanol was added and sonicated for 5 min to ensure complete solubilization of drug. After sonication, volume was made up to the mark with methanol. Filter the stock solution with whatman filter paper and the final filtrate is collected as sample stock solution.

### Chromatographic conditions

A BDS hypersil C<sub>18</sub> (250\*4.6 mm, 5 µm) column was used as the stationary phase. A mixture of buffer (pH 3.0) and methanol in the ratio of (50:50 %v/v) was used as a mobile phase and pH 3.0 adjusted with ortho phosphoric acid. It was filtered through 0.45µ (micron) membrane filter and degassed. The mobile phase was pumped at 1.0 ml/min. The eluents were monitored at 224 nm. The injection volumes of sample and standard were 20µl (microliter). Total run time is 10 min.

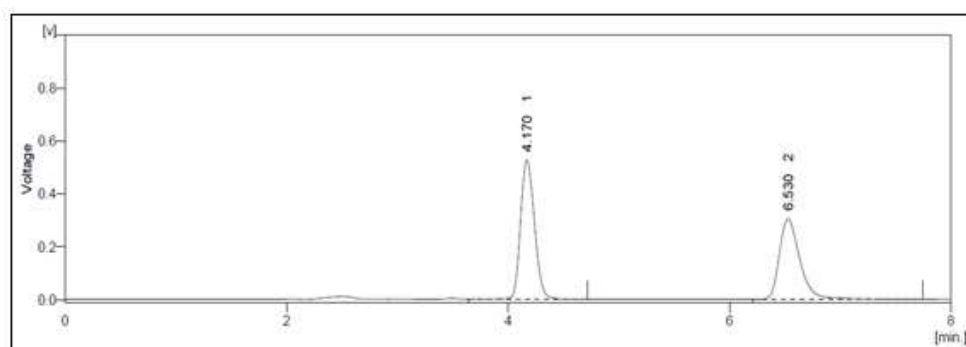


Fig. 3: Chromatogram of sacubitril and valsartan

The developed Method was validated for linearity, precision, accuracy, robustness and is applied for forced degradation studies as per the ICH guidelines [18-23]

## RESULTS AND DISCUSSION

### Method validation

The described method has been validated which include parameters

like system suitability, linearity, accuracy, precision, robustness, LOD (limit of detection) and LOQ (limit of quantification).

### System suitability

System suitability and chromatographic parameters were validated such as resolution, theoretical plates, and the tailing factor was calculated. The results are given in table 1.

Table 1: System suitability parameters for sacubitril and valsartan

System suitability parameter	Sacubitril	Valsartan
Retention time (min)	4.170	6.530
Theoretical plate number (N)	4915	6320
Tailing factor (T)	1.313	1.523
Resolution(R)	8.332	

### Linearity

The linearity of this method was evaluated by linear regression analysis and calculated by the least square method and studied by preparing standard solutions of sacubitril and valsartan at different

concentration levels. The calibration curve showed (Fig. 4 and 5) good linearity in the range of 12.25-36.75 µg/ml, for sacubitril with a correlation coefficient ( $r^2$ ) of 0.999 and 12.75-38.25 µg/ml for valsartan with a correlation coefficient ( $r^2$ ) of 0.999. Results are given in table 2.

Table 2: Linearity data for sacubitril and valsartan

Drug	Conc* (µg/ml)	Area
Sacubitril	12.25	2240.161
	18.375	3307.088
	24.5	4521.210
	30.625	5566.676
	36.75	6772.742
Valsartan	12.75	1878.693
	19.125	2773.397
	25.5	3791.580
	31.875	4668.280
	38.25	5679.762

Conc\*-concentration

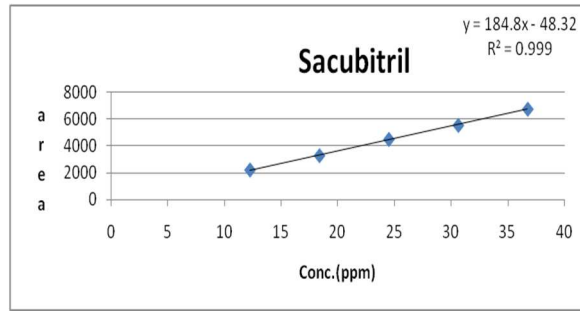


Fig. 4: Calibration curve of sacubitril

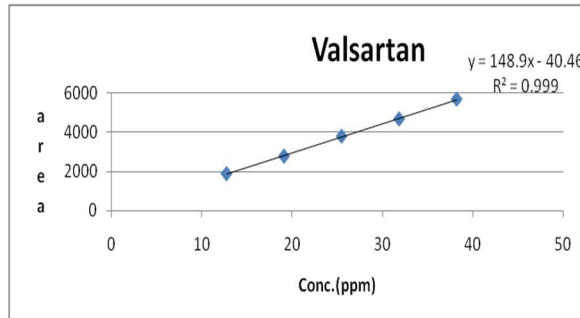


Fig. 5: Calibration curve of valsartan

#### Accuracy

Recovery studies were carried out by addition of the standard drug to the sample at 3 different concentration levels (80%, 100% and 120%) taking into consideration percentage purity of added bulk drug samples. At each concentration, the sample was injected thrice

to check repeatability and from the % RSD values it was analyzed that the method was accurate as % recovery values found to be in the range of 99.72-100.02% for the Sacubitril and 99.87-100.17 % for valsartan at three different concentrations 80%, 100%, 120%.

The results are given in table 3 and 4.

Table 3: Accuracy data for sacubitril

Conc* (%)	Sample amount (µg/ml)	Amount added (µg/ml)	Amount recovered (µg/ml)	% recovery	%mean recovery±SD*
80%	12.25	9.8	9.674	98.71	99.61±0.79
	12.25	9.8	9.796	99.96	
	12.25	9.8	9.816	100.16	
100%	12.25	12.25	12.129	99.01	99.57±0.53
	12.25	12.25	12.259	100.07	
	12.25	12.25	12.203	99.61	
120%	12.25	14.7	14.694	99.96	99.59±0.41
	12.25	14.7	14.574	99.14	
	12.25	14.7	14.650	99.66	

SD\*-standard deviation, Conc\*-concentration, Number of experiments (n)-3

Table 4: Accuracy data for valsartan

Conc* (%)	Sample amount (µg/ml)	Amount added (µg/ml)	Amount recovered (µg/ml)	% recovery	% mean recovery±SD*
80%	12.75	10.2	10.067	98.70	99.92±1.13
	12.75	10.2	10.294	100.92	
	12.75	10.2	10.215	100.15	
100%	12.75	12.75	12.622	99.00	99.63±0.65
	12.75	12.75	12.88	100.30	
	12.75	12.75	12.699	99.60	
120%	12.75	15.3	15.317	100.11	99.63±0.49
	12.75	15.3	15.168	99.13	
	12.75	15.3	15.247	99.65	

SD\*-standard deviation, Conc\*-concentration, Number of experiments (n)-3

**Precision****Repeatability**

A standard solution containing sacubitril (24.5 µg/ml) and valsartan (25.5 µg/ml) was injected six times and areas of peaks were measured and % RSD was calculated. The results are given in table 5.

**Intraday precision**

A standard solution containing (12.25,24.5,36.75 µg/ml) of

sacubitril and (12.75,25.5,38.25 µg/ml) of valsartan were analyzed three times on the same day and % R. SD was calculated. The results are given in table 6.

**Interday precision**

A standard solution containing (12.25, 24.5, 36.75µg/ml) of sacubitril (12.75, 25.5, 38.25 µg/ml) of valsartan were analyzed three times on a different day and % RSD was calculated. The results are given in table 7.

**Table 5: Repeatability data for sacubitril and valsartan**

Drug	Conc* (µg/ml)	Area	Mean±SD*(n=6)	% RSD*
Sacubitril	24.5	4503.25	4506.15±25.56	0.57
		4457.79		
		4521.20		
		4530.26		
		4507.76		
		4516.61		
Valsartan	25.5	3776.45	3772.76±32.26	0.86
		3784.03		
		3708.86		
		3799.17		
		3780.24		
		3787.81		

SD\*-standard deviation, RSD\*-relative standard deviation, Conc\*-concentration, Number of experiments (n)-6

**Table 6: Intraday data for sacubitril and valsartan**

Drug	Conc* (µg/ml)	Area mean±SD* (n=3)	% RSD*
Sacubitril	12.25	2223.62±15.41	0.63
	24.5	4475.65±51.86	1.16
	36.75	6728.43±32.64	0.49
Valsartan	12.75	1858.60±20.77	1.12
	25.5	3745.33±51.48	1.37
	38.25	5617.50±69.47	1.24

SD\*-standard deviation, RSD\*-relative standard deviation, Conc\*-concentration, Number of experiments (n)-3

**Table 7: Interday data of sacubitril and valsartan**

Drug	Conc* (µg/ml)	Area mean±SD* (n=3)	% RSD*
Sacubitril	12.25	2218.93±17.50	0.79
	24.5	4480.94±30.84	0.69
	36.75	6727.83±20.15	0.30
Valsartan	12.75	1850.82±28.78	1.55
	25.5	3732.18±63.54	1.70
	38.25	5619.57±45.30	0.81

SD\*-standard deviation, RSD\*-relative standard deviation, Conc\*-concentration, Number of experiments (n)-3

**Robustness**

Small deliberate changes in chromatographic conditions such as a change in mobile phase ratio (+2 %), change in pH (±2 units) and

flow rate (±2 units) were studied to determine the robustness of the method. The results were in the factor of (% RSD<2%) the developed RP-HPLC method for the analysis of sacubitril and valsartan. The results are given in table 8 and 9.

**Table 8: Robustness data for sacubitril**

Drug	Area at flow rate (-0.2 ml/min)	Area at flow rate (+0.2 ml/min)	Area at pH (-0.2)	Area at pH (+0.2)	Area at mobile phase(-2)	Area at mobile phase (+2)
Sacubitril	4628.12	4366.85	4577.39	4252.50	4580.41	4334.83
	4688.80	4417.00	4643.53	4326.41	4629.58	4408.15
	4706.76	4435.21	4661.51	4353.43	4656.83	4439.65
% RSD*	0.88	0.80	0.96	1.21	0.84	1.22

RSD\*-relative standard deviation, Number of experiments (n)-3

Table 9: Robustness data for valsartan

Drug	Area at flow rate (-0.2 ml/min)	Area at flow rate (+0.2 ml/min)	Area at pH (-0.2)	Area at pH (+0.2)	Area at mobile phase (-2)	Area at mobile phase (+2)
Valsartan	3917.08	3681.51	3879.05	3605.61	3875.17	3674.13
	3827.40	3601.23	3894.17	3526.61	3777.54	3696.78
	3947.18	3719.47	3909.24	3650.86	3909.63	3723.20
% RSD*	1.60	1.65	0.39	1.75	1.78	0.66

RSD\*-relative standard deviation, Number of experiments (n)-3

#### Limit of detection (LOD) and limit of quantification (LOQ)

The LOD and LOQ were found to be 0.85µg/ml and 2.580µg/ml for sacubitril and 0.89µg/ml and 2.687µg/ml for valsartan estimated by

using the standard formulas. The low values of LOD and LOQ illustrate that the developed method was sensitive, accurate and precise as it can detect and quantify with very low concentration. The result is given in table 10.

Table 10: LOD and LOQ data for sacubitril and valsartan

Drug	LOD*	LOQ*
Sacubitril	0.85(µg/ml)	2.580(µg/ml)
Valsartan	0.89(µg/ml)	2.687(µg/ml)

LOD\*-limit of detection, LOQ\*-limit of quantification

#### Method development

ICH prescribed stress conditions such as acidic, basic, oxidative, thermal and photolytic stresses were carried out.

#### Acid degradation

Acid decomposition studies were performed by refluxing 1 ml of sample stock solution was transferred into 10 ml of volumetric flask. 2 ml of 0.1 N HCl solutions were added and mixed well and put for 4 h at 70 °C 250 ml round bottom flask. After a time period, the content was cooled to room temperature. Then the volume was adjusted with diluent to get 24.5µg/ml for sacubitril and 25.5µg/ml for valsartan. After making final solutions, it is injected into HPLC

and the peak area and peak shapes were observed. Chromatogram of acid degradation on sample solution is shown below in fig. 6.

#### Base degradation

Basic decomposition studies were performed by refluxing 1 ml of sample stock solution was transferred into 10 ml of volumetric flask. 2 ml of 0.1 N NaOH solutions were added and mixed well and put for 4 h at 70 °C 250 ml round bottom flask. After a time period the content was cooled to room temperature. Then the volume was adjusted with diluent to get 24.5µg/ml for sacubitril and 25.5µg/ml for valsartan. After making final solutions, it is injected into HPLC and the peak area and peak shapes were observed. Chromatogram of base degradation on sample solution is shown below in fig. 7.

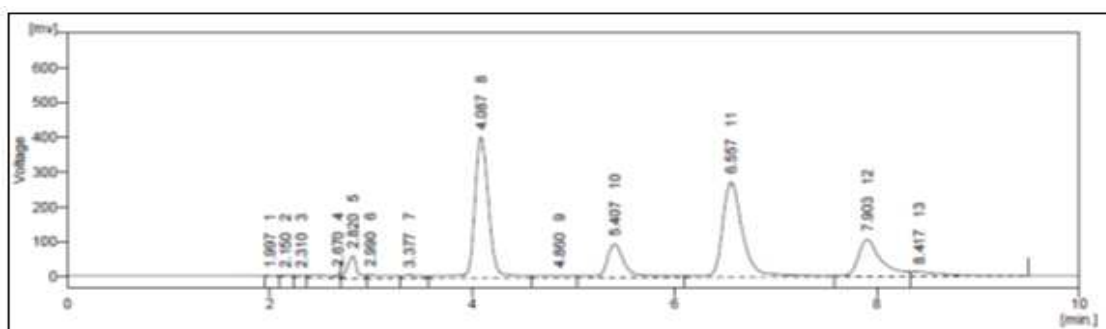


Fig. 6: Sacubitril and valsartan acid degradation sample at 4 h

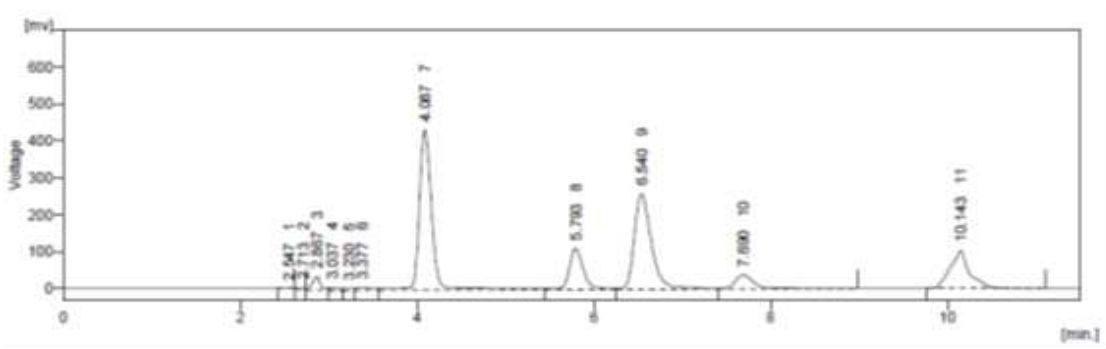


Fig. 7: Sacubitril and valsartan base degradation sample at 4 h

**Oxidative degradation**

Oxidative decomposition studies were performed by refluxing 1 ml of sample stock solution was transferred into 10 ml of volumetric flask. 2 ml of 3% H<sub>2</sub>O<sub>2</sub> solutions was added and mixed well and put for 4 h at 70 °C 250 ml round bottom flask. After a time period, the

content was cooled to room temperature. Then the volume was adjusted with diluent to get 24.5µg/ml for sacubitril and 25.5µg/ml for valsartan. After making final solutions, it is injected into HPLC and the peak area and peak shapes were observed. Chromatogram of oxidative degradation on sample solution is shown below in fig. 8.

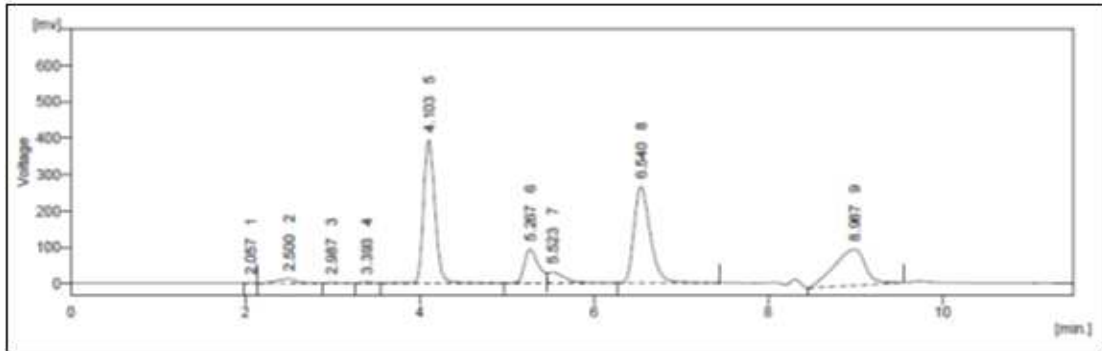


Fig. 8: Sacubitril and valsartan oxidation degradation sample at 4 h

**Thermal degradation**

Thermal degradation studies were performed by taking 1 ml of sample stock solution was transferred into 10 ml of volumetric flask. The volumetric flask was stored in an oven at 110 °C for 4 h. Then

the volume was adjusted with diluent to get 24.5µg/ml for sacubitril and 25.5µg/ml for valsartan. After making final solutions, it is injected into HPLC and the peak area and peak shapes were observed. Chromatogram of thermal degradation on sample solution is shown below in fig. 9.

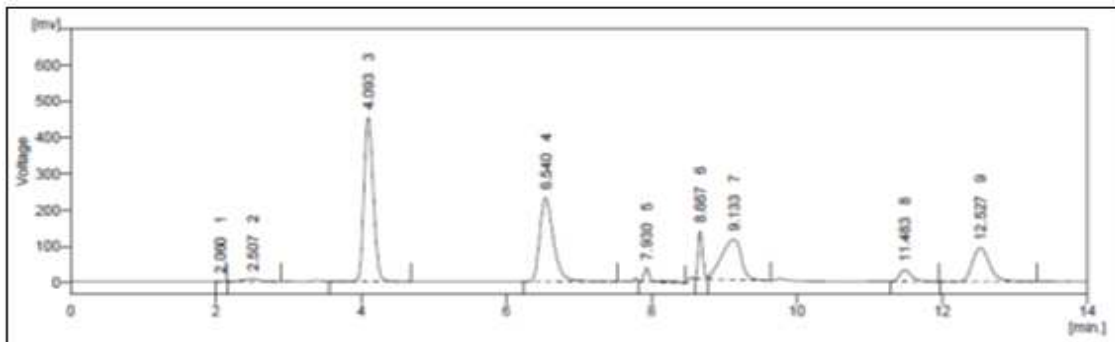


Fig. 9: Sacubitril and valsartan thermal degradation sample at 4 h

**Photolytic degradation**

Photo degradation studies were performed by taking 1 ml of sample stock solution was transferred into 10 ml of volumetric flask. The volumetric flask was kept in UV chamber for 72 h. Then the volume

was adjusted with diluent to get 24.5 µg/ml for sacubitril and 25.5µg/ml for valsartan. After making final solutions it is injected into HPLC and the peak area and peak shapes were observed. Chromatogram of photo degradation on sample solution is shown below in fig. 10.

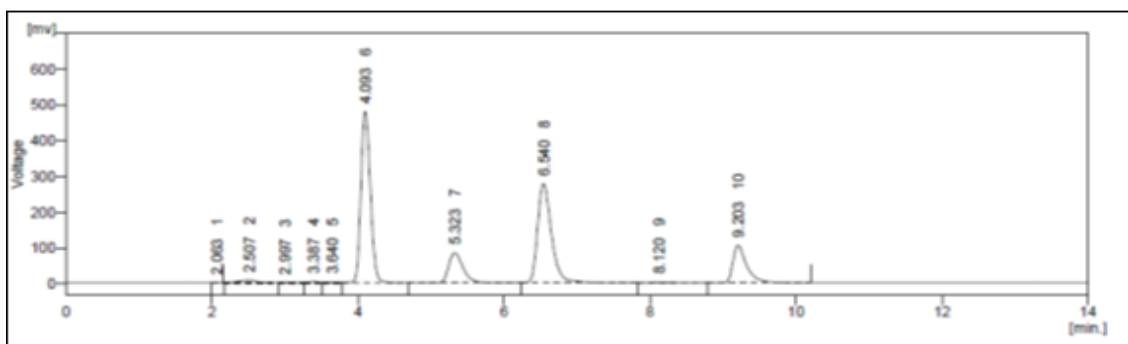


Fig. 10: Sacubitril and valsartan photo degradation sample at 72 h

Table 11: Stability data for sacubitril and valsartan

Sacubitril standard area for stability-4827.067				
Parameter	Standard		Sample	
	Area	% degradation	Area	% degradation
Acid	3613.169	25.148	3885.979	19.496
Base	3937.527	18.428	4059.528	15.901
Oxidation	3638.838	24.616	3645.262	24.483
Thermal	3930.438	18.575	4050.228	16.093
Photo	4184.313	13.316	4330.211	10.293
Valsartan standard area for stability-4160.168				
Parameter	Standard		Sample	
	Area	% degradation	Area	% degradation
Acid	3607.113	13.294	3743.630	10.013
Base	3355.132	19.351	3474.849	16.473
Oxidation	3613.807	13.133	3459.645	16.839
Thermal	3069.332	26.221	3026.332	27.255
Photo	3612.071	13.175	3654.960	12.144

Sacubitril and valsartan undergoes significant degradation in acid, base, peroxide, thermal and UV. Comparatively, more degradation was found with acid and peroxide for sacubitril and with thermal for valsartan. Hence, a method of the analysis of sacubitril and valsartan in tablet dosage form shows that the degradation product doesn't interfere with the analytical determination. Hence the proposed analytical method is also useful for the determination of sacubitril and valsartan stability in a sample of the pharmaceutical dosage form.

#### CONCLUSION

Stability indicating RP-HPLC methods have been developed and validated for the determination of sacubitril and valsartan in tablet dosage form. The methods are found to be specific as there was no interference of any co-eluting impurities after stress degradation study. The degraded products are well resolved, indicating the method can also be useful for determination of degraded products. The proposed method is found to be simple, accurate, precise and robust. Hence, it can be used successfully for the routine analysis of sacubitril and valsartan in pharmaceutical dosage forms and for analysis of stability samples obtained during accelerated stability study.

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#### CONFLICT OF INTERESTS

Declare none

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