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RESEARCH ARTICLE

VALIDATION OF STABILITY INDICATING RP-HPLC METHOD FOR THE SIMULTANEOUS ESTIMATION CONTENT AND IMPURITIES OF NURTEC ODT(RIMEGEPANT SULFATE ORALLY DISINTEGRATING TABLETS) IN BULK AND PHARMACEUTICAL DOSAGE FORM

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Abstract

A simple, accurate, precise, and rapid stability indicating reverse phase A performance liquid chromatography method was used for the estimation of rimegepant sulfate orally disintegrating tablets in bulk and oral dosage form. The proposed analytical method has been validated for content and impurities of specificity, linearity, accuracy, precision, and robustness. The chromatography was achieved in an Agilent Eclipse XDB-C18 (length 150 x diameter 4.6 mm, particle size 5µm) column with gradient flow. The optimal chromatographic condition consisted of mobile phase with a flow rate of 1.0 mL/min, a column temperature of 30 °C, a run time of 25 minutes, and a detector wavelength of 265 nm.

Introduction:-

Rimegepant sulfate, known under the brand name Nurtec ODT, is used to treat the acute treatment of migraine with or without aura in adults and the preventive treatment of episodic migraine in adults. [1,2]. Migraine is one of the most common chronic neurologic diseases[3]. The illness is marked by recurrent headaches that range in intensity from mild to severe, as well as nausea, photophobia, phonophobia, cutaneous allodynia, and other phobias. [4, 5] The headache attack lasts anywhere from 4 to 72 hours and happens once or twice per month on average. It is the third most prevalent and the second most incapacitating. most common neurological illnesses, which affect 12% of men and 33% of women for the rest of their lives [6, 7]. The name migraine is taken from the Greek word "hemikrania," which was eventually changed to the Latin word "hemigranea." Such a word is translated as "migraine" in French. It frequently results in disability and job loss[8]. Migraines can be classified into subtypes according to the headache classification committee of the International Headache Society[9,10]. Genes play a significant role in migraine. There was no discernible pattern of heredity, however, relatives of patients have a three times higher risk of developing migraines than relatives of healthy participants[11, 12, 13, 14].

After carefully reading the literature, no analytical technique for calculating rimegepant sulfate in bulk and tablet impurities was published; only the estimation of rimegepant in bulk and tablets using content estimation[15, 16]was reported. To the best of the authors' knowledge, no stability-indicating related substance method has been documented in the literature for determining RM in bulk or its tablets. In order to achieve this goal, the current study aims to design and validate a quick and easy RP-HPLC-PDA method for the quantification of RM. See the reference structure. Figs 1, 2, 3, and 4.

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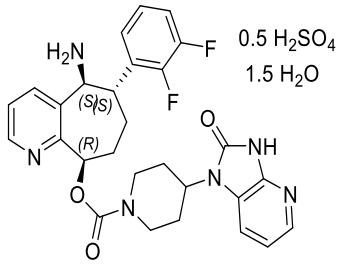


Figure. 1:- Structure ofRimegepant Sulfate (RM).

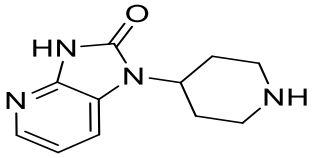


Figure. 2: - Structure of RMM-4.

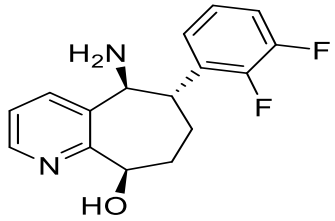


Figure. 3:- Structure of RM-9.

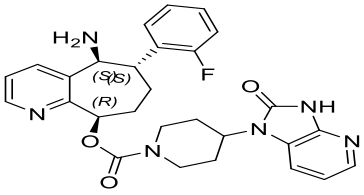


Figure. 4:- Structure of RM-E.

Materials and Methods:-

Rimegepant sulfate drug substance, working standard, and finished dosage forms were manufactured by Changzhou Pharmaceutical Factory, China. Other chemicals, such as trifluoracetic acid, were of analytical grade. Methanol (Tedia), acetonitrile (Sigma), and Milli-Q water were used for the mobile phase and diluent preparations.

Instrument Details:

HPLC Shimadzhu LC20, with a PDA detector, and Empower 3 software were used for the purpose of method development and validation. This HPLC is comprised of a quaternary pump. Analytical balance (Mettler Toledo) and pH meter (Thermo).

Method development and cinematographic conditions:

Various mobile phase types were investigated in the development of a stability-indicating LC method for the analysis of rimegepant sulfate orally disintegrating tablets. The suitability of the mobile phase was decided on the basis of the selectivity and sensitivity of the impurities, stability studies, and separation among impurities formed during forced degradation studies.

Finally, good separations were achieved in the Agilent Eclipse XDB C18 (150 x 4.6 mm, 5µm) analytical column. The mobile phase, with a flow rate of 1.0 mL/min, consisted of mobile phase A: 0.05% TFA in water (100%), and mobile phase B: 0.05% TFA in acetonitrile (100%). The gradient is as mentioned in **Table 1.** The mobile phase was degassed and filtered using a 0.45µm membrane filter. The flow rate is 1.0 mL/min with an injection volume of 10µL. The analysis was performed at a column temperature of 30°C with the detection at wavelength of 265nm

(Rimegepant Sulfate). For complete extraction of actives from formulations, trials were taken and 50% methanol was finalized as diluent. See the gradient program in reference table.1.

Table 1:- Mobile phase gradient program for the chromatographic method.

Time (min)	Mobile Phase A	Mobile Phase B
0.0	95	5
3.0	70	30
15.0	40	60
15.1	95	5
25.0	95	5

Solution preparations:

Preparation of Standard Solution:

Accurately weigh about 8.5mg of Rimegepant sulfate (Eq. Rimegepant) working standard, which were weighed and taken into a 100 mL volumetric flask. To this, add 10 mL of methanol, sonicate to dissolve completely, then dilute to volume with methanol, and mix well. Further, take 2 mL of this solution into a 100 mL volumetric flask, then dilute to volume with diluent and mix well (the concentration of rimegepant sulfate is 1.5µg/mL).

System suitability test solution:

Impurity mix stock solution:

Weighed an accurately each impurity of RMM-4, RM-9 and RM-E into a 100mL of volumetric flask then to this add 10mL of methanol and sonicate to dissolves then dilute to volume with diluent and mix well.

Accurately weigh about 84mg of Rimegepant sulfate (Eq. Rimegepant) working standard, which were weighed and taken into a 100 mL volumetric flask to this added each 2mL of RMM-4, RM-9 and RM-E impurities stock solution and add 10 mL of methanol, sonicate to dissolve completely, then dilute to volume with methanol, and mix well. (The concentrations are respectively, RM, RMM-4, RM-9 and RM-Eis0.750µg/mL, 1.5µg/mL, 1.5µg/mL, and 1.5µg/mL).

Preparation of sample solution:

Select the tablets randomly and weigh 20; crush to a fine powder; take a fine powder equivalent (75mg of rimegepant) and place in a 100 mL volumetric flask containing 50 mL of diluent and sonicate for 15 minutes with intermediate shaking; then cool to room temperature, then dilute to volume with diluent, and mix well. Centrifuge the solution at 10000 rpm for 10 minutes, then take the clear supernatant solution as a sample solution.

Analytical Method Validation:

The optimized chromatographic conditions were validated for assay and impurities of rimegepant sulfate in rimegepant orally disintegrating tablets by evaluating specificity, linearity, precision, accuracy, robustness and system suitability parameters in accordance with the ICH guideline Q2 (R1).[17,18,19,20]

Specificity:

Specificity-Blank and Placebo interference:

To establish the interference of blank, placebo, degradation impurities, study was conducted. Assay and impuritieswere performed on placebo in duplicate equivalent to concentration of test preparation as per proposed method. Established the degradation studies on different conditions and reported mass balance.

Linearity:

For Assay: Establish the linearity by plotting a graph of concentration versus peak response and determining the correlation coefficient, slope, and Y-intercept. A series of solutions of RM, the standard solutions, were prepared in the concentration range of 37.5µg/mL to 187.5µg/mL.

For degradation impurities, establish linearity by plotting a graph of concentration versus peak response and determining the correlation coefficient, slope, and Y-intercept. In a series of solutions of RM, RMM-4, RM-9, and RM-E, the concentrations range from its specification level of 0.2%, i.e., LOQ to 0.24%.

Method Precision and Intermediate Precision:
The precision study was confirmed by preparing six preparations, and the %RSD of six assay values obtained was calculated.

The precision study was confirmed by preparing six preparations, and the %RSD of six unspiked sample and spiked sample values obtained was calculated.

Accuracy:
The (%) assay recovery level of rimegepant sulfate from spiked placebo was confirmed at three different spike levels, i.e., 50%, 100%, 150 %, and 200%. Samples were prepared by mixing placebo with rimegepant sulfate drug substances equivalent to the test concentration. Sample solutions were prepared in triplicate for each spike level, and (%) recovery and (%) RSD were calculated.

The (%) impurities recovery level of rimegepant sulfate from spiked placebo was confirmed at three different spike levels, i.e., 0.05%, 0.16%, 0.20 %, and 0.24%. Samples were prepared by finished product equivalent to the test concentration. Sample solutions were prepared in triplicate for each spike level, and (%) recovery and (%) RSD were calculated.

Solution Stability:
Conducted the solution stability tests of standard and sample solutions at room temperature and under refrigerator conditions, as per the proposed assay method. The % difference between the areas obtained for rimegepant sulfate at the initial and different time intervals should not be more than 2.0, and as well as the impurity method, there are no other impurities found. So, the sample and standard solutions were stable for up to 48 hours at room temperature.

Robustness:
The robustness studies were evaluated by deliberate changes in chromatographic conditions. The conditions studied were flow rate (altered by ±0.10 mL/min), wavelength (altered by ±2 nm), variation in mobile phase compositions, and column oven temperature (±5°C). A standard solution was prepared and injected into the HPLC system. The system suitability parameters were evaluated for each deliberate variation.

System suitability:
System suitability testing is an integral part of liquid chromatographic method validation and is performed to check and ensure the on-going performance of a chromatographic system. The system suitability was estimated by five replicate injections of standard solution at 100% of the test concentration and also by two injections of check standard solutions. The column efficiency as determined from rimegepant sulfate peak is not less than 2000 USP plate counts, the USP tailing for the same peaks is not more than 2.0, the %RSD for corresponding peak areas of five for the assay and six for the impurity test replicate injections of the standard solution should not be more than 2.0%, and the similarity factor between the standard solution and the check standard solution should be 0.98 to 1.02 for the assay test.

Results and Discussion:-

Analytical Method Validation:
The content test method was validated for specificity, linearity, precision, accuracy (recovery), solution stability, robustness, and system suitability and was found to be meeting the predetermined acceptance criteria.

Specificity:
Specificity-blank and placebo interference:
Interference study:
From the chromatograms of blank, placebo, and degradation impurity solutions, there is no inference at the retention time of rimegepant peak. The chromatogram of the blank, placebo, standard, and sample using the proposed method is shown in Figures 5, 6, 7,8 and 9.

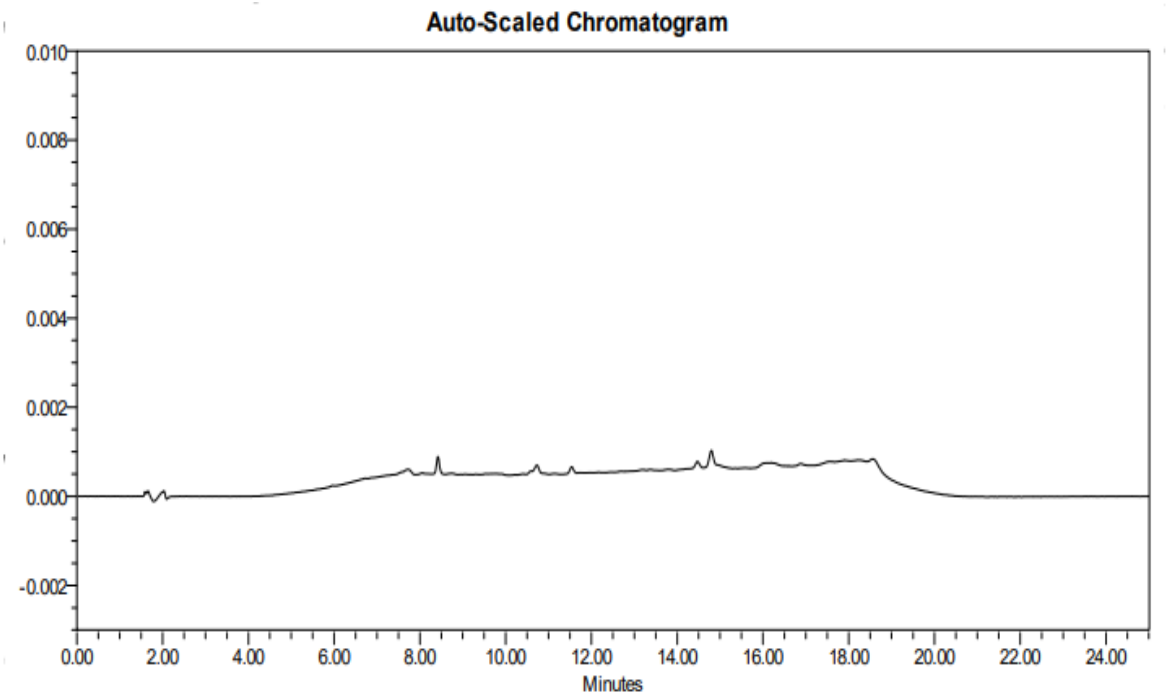


Figure 5: - (Blank solution Chromatogram).

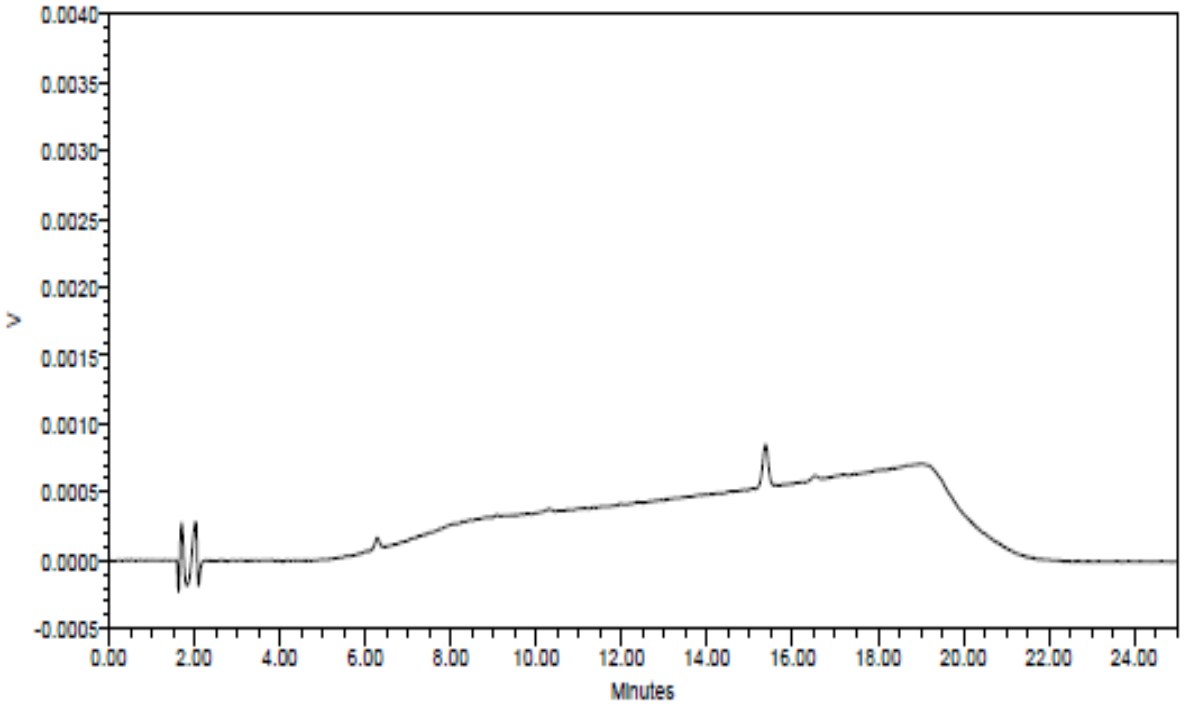


Figure 6: - (Placebo solution Chromatogram).

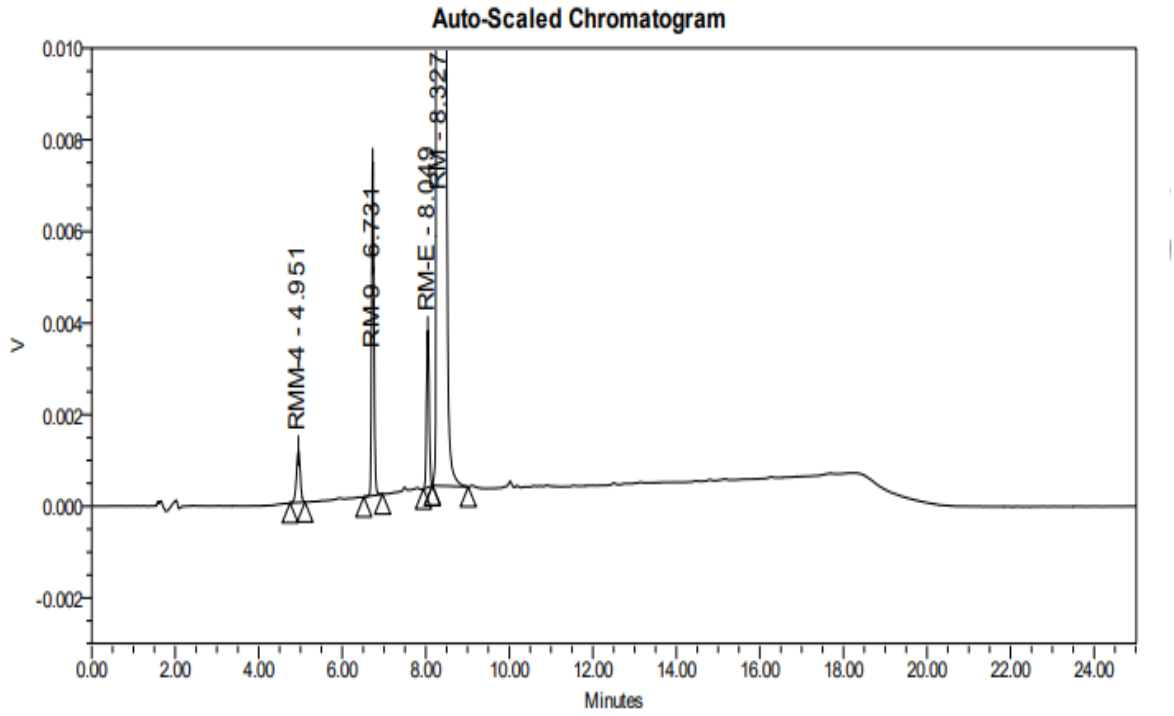


Figure 7:- (System suitability chromatogram).

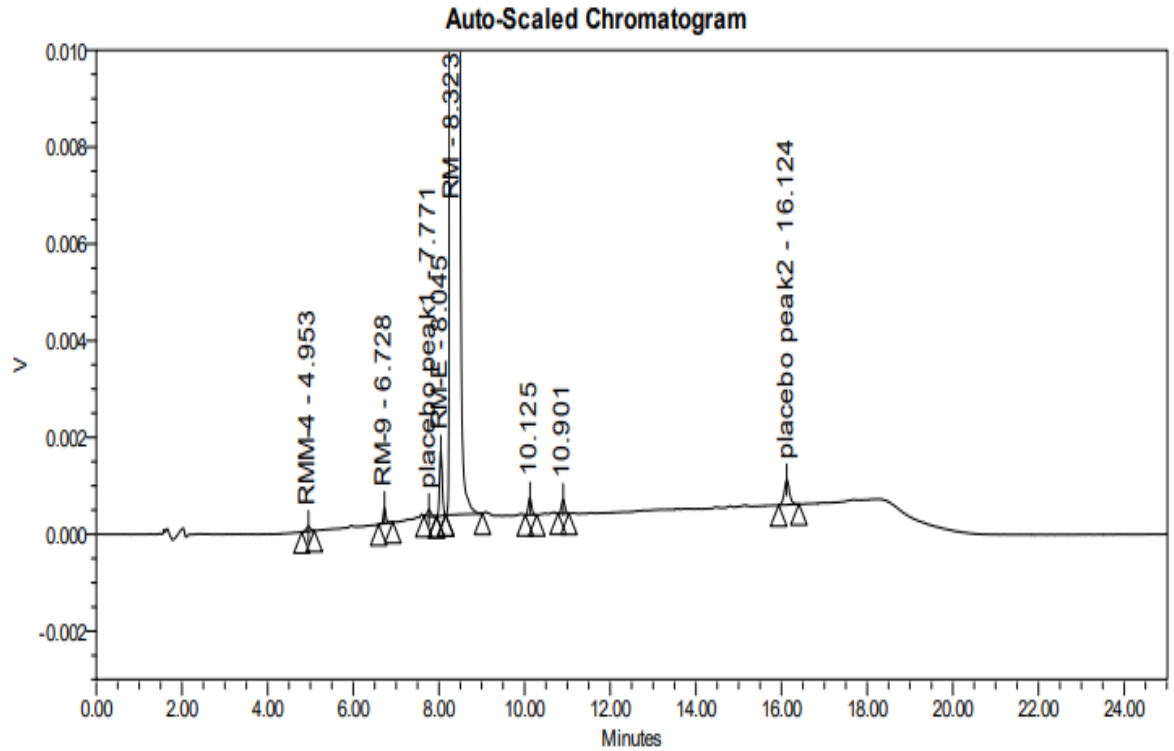


Figure 8:- (Control sample chromatogram).

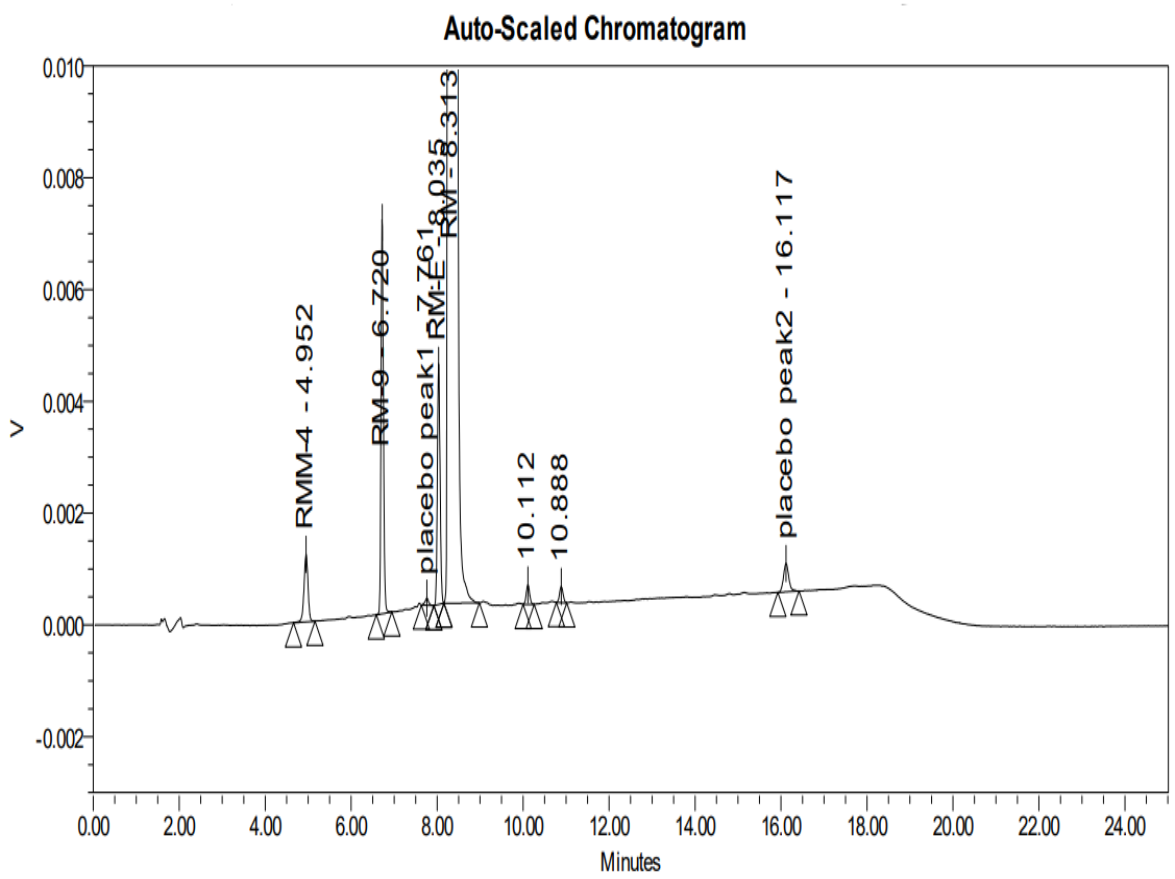


Figure 9:- (Spikes sample chromatogram).

Force degradation study:

Table 2:- Degradation results summary.

Rimegepant sulfate (RM) in finished product assay and related substances degradation results						
Degradation Conditions		**Degradation Content (%)**	**Total Degradation**	**(%) Mass Balance**	**Purity Angle**	**Purity Threshold**
Controlled Sample		100.0	0.16	100.2	0.133	0.289
Acid Degradation	1M HCl_3ml_2h	93.6	7.4	101.0	0.145	0.352
Base Degradation	1M NaOH_2ml_2h	100.1	0.20	100.3	0.122	0.551
Oxidation Degradation	3%H2O2_2ml_2h	99.6	0.26	99.9	0.161	0.325
Temperature (Solid)	60℃_solid_48h	99.4	0.66	100.1	0.221	0.452
Temperature (Liquid)	60℃_liquid_5h	100.4	0.32	100.7	0.152	0.365
Light (Solid)	4500lx_solid_48h	95.1	3.21	98.3	0.162	0.399
Light (Liquid)	4500lx_liquid_5h	101.1	0.15	101.3	0.146	0.299
Humidity	92.5% RH-48h	100.1	0.15	100.3	0.132	0.325

Rimegepant sulfate (RM) in finished product related substances impurities degradation results						
Degradation Conditions		**RMM-4**	**RM-E**	**RM-9**	**Unknown impurity**	**Total Degradation**
Controlled Sample		0.03	0.08	ND	0.05	0.16
Acid Degradation	1M HCl_3ml_2h	3.21	0.08	4.05	0.06	7.4
Base Degradation	1M NaOH_2ml_2h	0.05	0.09	ND	0.06	0.20
Oxidation Degradation	3%H2O2_2ml_2h	0.04	0.09	0.06	0.07	0.26

Temperature (Solid)	60℃_solid_48h	0.03	0.08	0.51	0.04	0.66
Temperature (Liquid)	60℃_liquid_5h	0.02	0.08	0.19	0.03	0.32
Light (Solid)	4500lx_solid_48h	1.47	0.09	1.61	0.04	3.21
Light (Liquid)	4500lx_liquid_5h	0.03	0.08	ND	0.04	0.15
Humidity	92.5% RH-48h	0.02	0.08	ND	0.05	0.15

Linearity:

The calibration curve obtained by the least squares regression analysis between peak area and concentration showed a linear relationship with a correlation coefficient of greater than 0.999 over the calibration ranges tested for both actives. A correlation was obtained between peak area and concentration of rimegepant sulfate (RM). Linearity graphs of RMM-4, RM-9, RM-E and RM are shown in Tables 3, 4, and 5.

Table 3:- Linearity Results for assay of rimegepant (RM).

(%) Level	Concentration (µg/mL)	Peak Area
50%	38.0104	493748
80%	60.8167	790600
100%	76.0209	989724
120%	91.2251	1180969
200%	152.0418	1980431
250%	190.0522	2474423
Intercept	-2797.9577	
Slope	13033.7263	
Correlation Coefficient	1.0000	

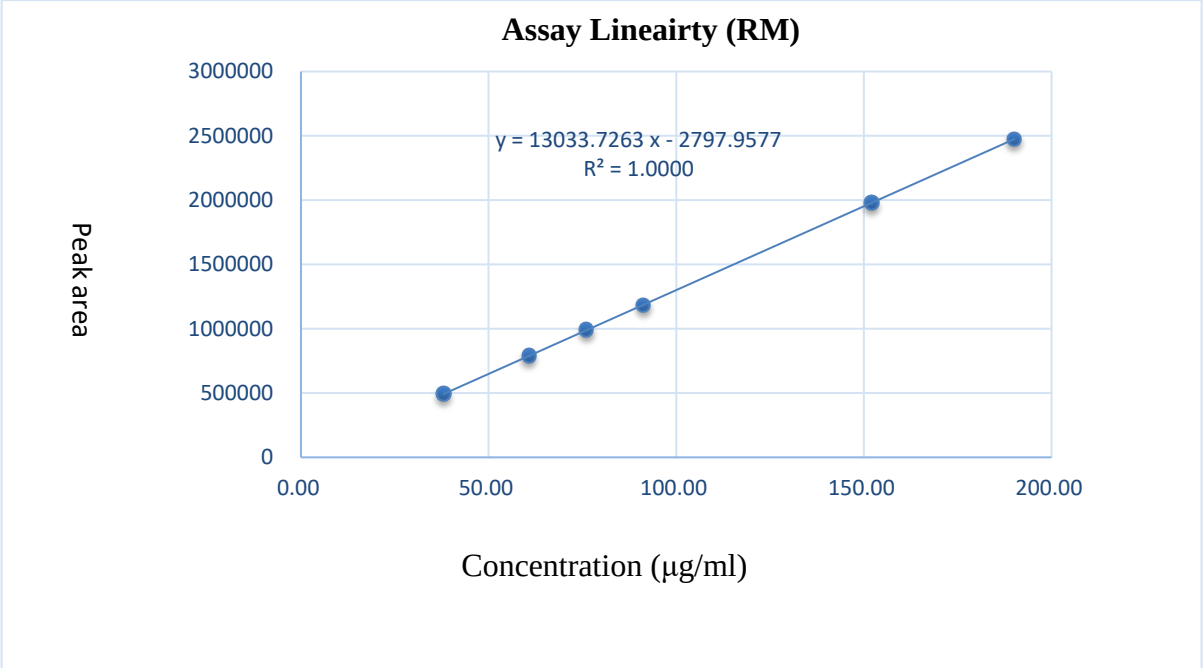
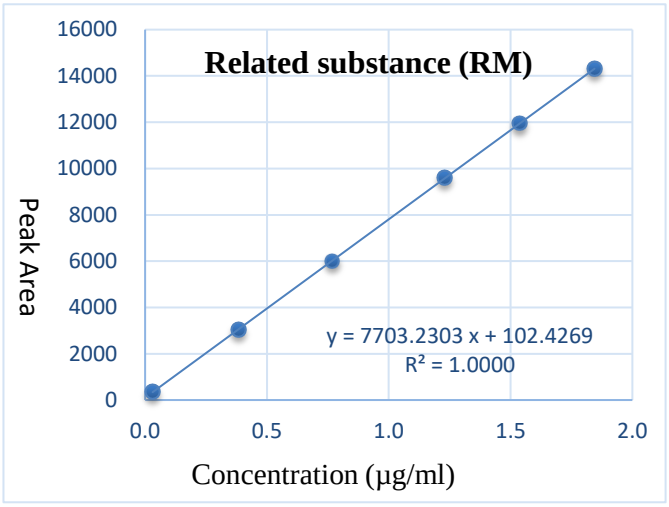
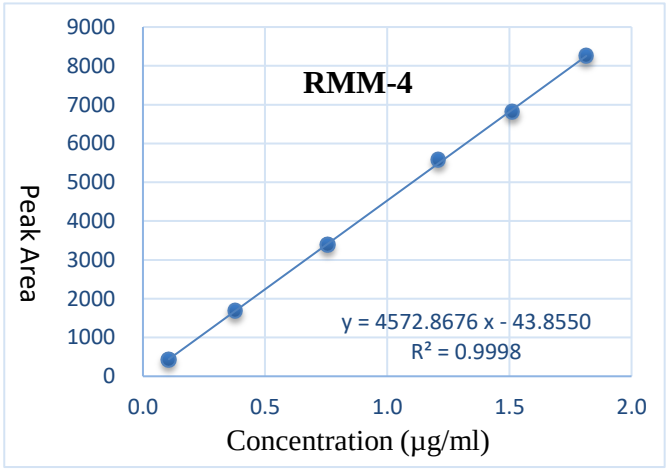


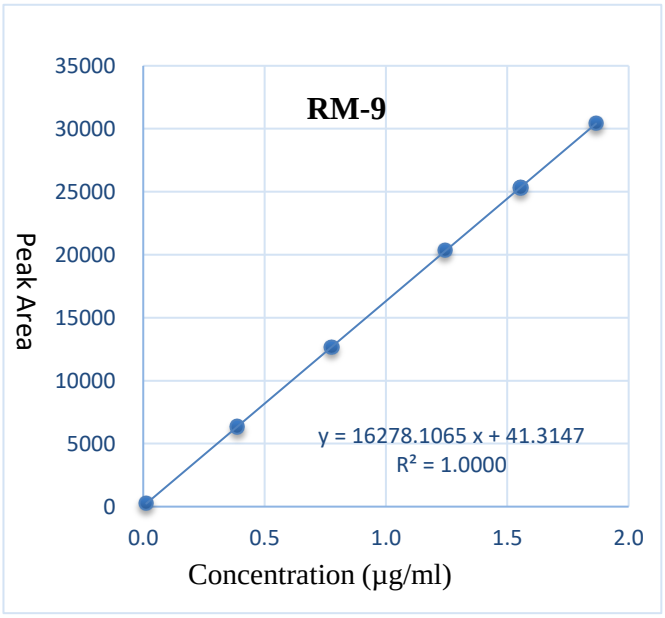
Table 4:- Linearity Results for Related Substances.

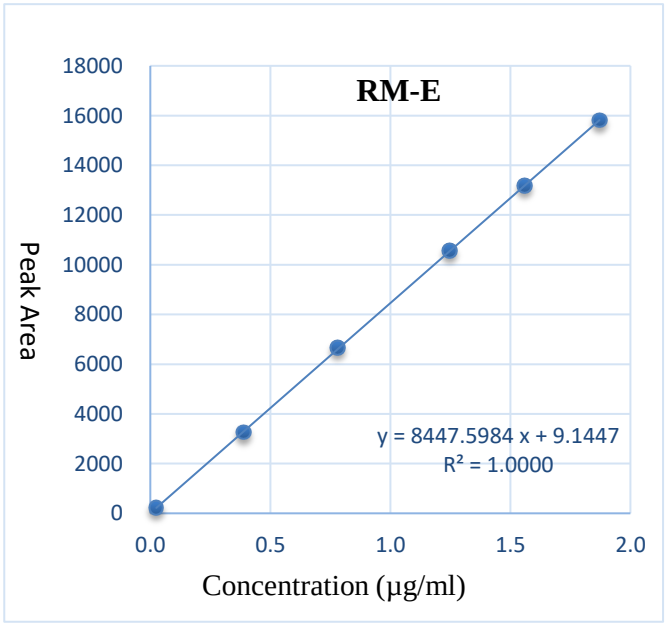
(%) Level	RM Concentration (µg/mL)	Peak Area	RMM-4 Concentration (µg/mL)	Peak Area	RM-9 Concentration (µg/mL)	Peak Area	RM-E Concentration (µg/mL)	Peak Area
LOQ	0.0307	368	0.1059	434	0.0124	260	0.0250	217
0.05%	0.3843	3034	0.3781	1686	0.3887	6360	0.3899	3258

0.10%	0.7687	6006	0.7563	3392	0.7774	12659	0.7798	6654
0.16%	1.2299	9590	1.2100	5574	1.2439	20355	1.2477	10566
0.20%	1.5373	11947	1.5125	6814	1.5549	25299	1.5596	13179
0.24%	1.8448	14315	1.8150	8258	1.8659	30432	1.8715	15797
Intercept	102.4269		-43.8550		41.3147		9.1447	
Slope	7703.2303		4572.8676		16278.1065		8447.5984	
Correlation Coefficient	1.0000		0.9999		1.0000		1.0000	
f	1.00		1.68		0.47		0.91	









Precision (Assay and Related substances):
For the assay, the precision of the proposed method was evaluated by carrying out six independent assays of test samples. %RSD of six assay values was calculated.The results are given in table 5.

For the organic impurities, the precision of the proposed method was evaluated by carrying out six spiked samples individually at specification level (0.2% w/w) from the same batch of RM tablets. The results of six samples were calculated by RM unknown impurity. See the results in table5.

Table. 5:- Precision results of (RMM-4, RM-9, RM-E, RM).

Impurity Name	Precision spiked (n=6)		LOQ Precision (n=6)	
	% Recovery	% RSD	% Recovery	% RSD
RMM-4	97.5	0.5	100.9	4.5
RM-9	99.8	0.3	104.5	2.0
RM-E	96.8	1.0	95.8	1.2
RM (Assay)	100.1	0.3	/	/

Accuracy:
The recovery of assay of RM and its impurities from a spiked placebo was conducted at four different spike levels i.e., 0.05%, 0.16%, 0.20%, and 0.24 %. Samples were prepared by mixing placebo with rimegepant sulfate (RM) drug substances equivalent to test concentration. Sample solutions were prepared in triplicate for each spike level and recovery (%), and RSD (%) were calculated. See the results in the Table 6.

Table 6:- Recovery results of (RMM-4, RM-9, RM-E, RM).

Impurity Name	Recovery (n = 3)[A]				Overall Mean (n = 12)[B]	% RSD (n = 12)[C]
	0.05%	0.16%	0.20%	0.24%		
RMM-4	100.5	98.1	97.1	97.3	98.3	1.6
RM-9	103.2	99.4	98.9	99.1	100.2	2.0
RM-E	96.8	95.8	96.9	96.2	96.4	0.5
RM (Assay)	100.4 (50%)	100.6 (100%)	100.8(150%)	100.3(200%)	100.5	0.2

[A]Mean recovery of four replicates at each concentration level (%).
[B]Overall mean recovery of the four different concentration levels (%).
[C]Relative standard deviation of all overall recoveries for the four different concentration levels.

Solution stability of assay:
The reference solution and the test sample solution considered, were respectively placed at room temperature and refrigerator for a period of about 48 hours. The results were given in Table 7,8.

Table 7:- Solution stability in reference solution.

Stability of reference solution rimegepant (RM)				
Time	(~25°C) Room Temperature		(~5°C) Refrigerator	
	% Of Assay	% Difference	% Of Assay	% Difference
0 hour	100.0	NA	100.0	NA
8 hours	100.6	0.6	100.2	0.2
12 hours	100.9	0.9	100.3	0.3
18 hours	100.2	0.2	100.1	0.1
36 hours	100.5	0.5	100.3	0.3
48 hours	100.6	0.6	100.6	0.6
51 hours	100.3	0.3	100.2	0.2

Table 8:- Solution stability in test solution.

Stability of Test solution rimegepant (RM)				
Time	(~25°C) Room Temperature		(~5℃) Refrigerator	
	% Of Assay	% Difference	% Of Assay	% Difference
0 hour	100.2	NA	100.2	NA
8 hours	100.2	0.0	99.9	0.3
12 hours	99.9	0.1	100.0	0.2
18 hours	99.8	0.2	100.1	0.1
36 hours	100.0	0.2	100.3	0.1
48 hours	100.2	0.0	99.8	0.4
51 hours	99.9	0.1	99.9	

Solution stability of related substances:

The reference solution and the test sample solution considered, were respectively placed at room temperature for a period of about 48 hours. The results were given in Table9,10 and 11

Table 9:- Solution stability results of unspiked sample @RT(RMM-4, RM-9, RM-E, RM).

Time	RMM-4(%)	RM-9(%)	RM-E (%)	(%) [A]SMI	(%) Total impurities
0h	0.02	0.01	0.09	0.03	0.17
9.5h	0.02	0.01	0.09	0.03	0.17
15.5h	0.02	0.01	0.09	0.03	0.17
20.5h	0.03	0.01	0.09	0.03	0.18
26h	0.03	0.01	0.09	0.03	0.18
32h	0.03	0.02	0.09	0.03	0.19
38h	0.03	0.02	0.09	0.03	0.20
42h	0.03	0.02	0.09	0.03	0.19
48h	0.03	0.02	0.09	0.03	0.19
56.5h	0.03	0.02	0.09	0.03	0.19
59h	0.03	0.02	0.09	0.03	0.19
60.3h	0.03	0.02	0.09	0.03	0.19
64.5h	0.03	0.02	0.09	0.03	0.19
68.5h	0.03	0.02	0.09	0.03	0.19

[A]Single maximum impurity

Table 10:- Solution stability results of spiked sample @RT (RMM-4, RM-9, RM-E, RM).

Time	RMM-4 (%)	RM-9 (%)	RM-E (%)	(%) [A]SMI	(%) Total impurities
0h	0.22	0.22	0.29	0.03	0.79
9.5h	0.23	0.22	0.29	0.03	0.80
15.5h	0.23	0.22	0.29	0.03	0.80
20.5h	0.23	0.22	0.29	0.03	0.80
26h	0.23	0.22	0.29	0.03	0.80
32h	0.23	0.22	0.29	0.03	0.80
38h	0.24	0.22	0.29	0.03	0.81
42h	0.24	0.22	0.29	0.03	0.81
48h	0.24	0.23	0.29	0.03	0.81
56.5h	0.24	0.23	0.29	0.03	0.82
59h	0.24	0.23	0.29	0.03	0.82
60.3h	0.24	0.23	0.29	0.03	0.82
64.5h	0.24	0.23	0.29	0.03	0.82
68.5h	0.24	0.23	0.29	0.03	0.83

[A]Single maximum impurity

Table 11:- Solution stability results of spiked sample @RT (RM).

Time	(~25°C) Room Temperature	
	% Of Assay	% Difference
0 hours	101.5	NA

7.5 hours	101.3	0.2
13 hours	101.1	0.4
19 hours	101.2	0.3
23.5 hours	101.3	0.2
29.5 hours	100.9	0.6
35.5 hours	100.8	0.7
41.5 hours	100.9	0.6
48.5 hours	100.6	0.9
67.5 hours	101.0	0.5
72.5 hours	101.1	0.4

Robustness:
The reference solution was injected in different conditions, and there are no abnormal results; in all the conditions, system suitability is good. The results are given in Table 12.

Table 12:- Robustness results of reference solution (RM).

Rimegepant sulfate (RM) related substances method					
Condition		Retention time	%RSD STD	Theoretical Plates	Tailing Factor
Normal Condition		8.662	0.8	94814	1.1
Flow	0.9ml/min	8.991	0.5	93862	1.1
	1.1 ml/min	8.144	0.5	95011	1.1
Wavelength	263 nm	8.612	0.3	94521	1.1
	267nm	8.621	0.2	96421	1.1
Column Temperature	25 ℃	8.752	0.6	90214	1.1
	35℃	8.552	0.8	88451	1.1
Organic phase % in mobile phase A	96:4	8.696	0.6	94412	1.1
	94:6	8.596	0.2	93412	1.1
TFA Concentration (%)	0.045	8.552	0.3	93412	1.1
	0.055	8.559	0.4	94214	1.1

Conclusion:-

The Validated HPLC results shows that the of rimegepant in bulk and tablets dosage forms. The method, specific, precise, robust, stable, and can be applied for the routine and stability analysis for commercially available formulation.

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