A NOVEL VALIDATED RP-HPLC METHOD FOR THE ESTIMATION OF REMDESIVIR IN BULK AND PHARMACEUTICAL DOSAGE FORM

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***ABSTRACT:** A stability indicating RP-HPLC method has been developed for quantification of Remdesivir in bulk and in pharmaceutical dosage form. The chromatographic analysis was accomplished at ambient temperature on Symmetry ODS (C18) RP Column, 250 mm x 4.6 mm, 5µm column and 1.0 mL/min flow rate by using Eluent composed of Phosphate Buffer (0.02M) and Acetonitrile in the ratio of 48: 52 (pH-2.80). The UV detection at the wavelength of 248 nm was carried out using 20µL injection volume. The Remdesivir retention time was found to be 3.665 minute. The method in the range of 30-70µg/mL was found to be linear (R2 = 0.999) with a detection limit and quantitation limit of 0.09 and 0.27 µg/mL, respectively. The mean recovery% over the three tested levels of 80, 100 and 120% were found to be 100.39, 99.98, and 100.31%, respectively. The mean %assay of 99.69 for method repeatability and 0.20 for intermediate precision were found with %RSD of 1.00 and 0.926, respectively. Remdesivir drug substance and their product exposed to acid, alkali, oxidative, thermal, and photolytic stress conditions. The method as per ICH guidelines was validated for specificity, linearity, detection limit, quantitation limit, precision, accuracy, robustness, solution stability, and can be effectively used for routine analysis.*
***Key Words:** Remdesivir, RP-HPLC, Accuracy, Precision, Robustness, ICH Guidelines.*

I. INTRODUCTION

Remdesivir is an antiviral nucleotide analogue used for therapy of severe novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome (SARS) coronavirus 2 (CoV-2) infection. Remdesivir therapy is given intravenously for 5 to 10 days and is frequently accompanied by transient, reversible mild-to-moderate elevations in serum aminotransferase levels but has been only rarely linked to instances of clinically apparent liver injury, its hepatic effects being overshadowed by the systemic effects of COVID-19. Remdesivir[1] is indicated for the treatment of adult and pediatric patients aged 12 years and over weighing at least 40 kg for coronavirus disease 2019 (COVID-19) infection requiring hospitalization. It is also indicated for the treatment of non-hospitalized patients with mild-to-moderate COVID-19, who are at high risk for progression to severe COVID-19, including hospitalization or death. Remdesivir is a nucleoside analog used to inhibit the action of RNA polymerase. The duration of action is moderate, as it is given once daily. Due to much higher selectivity of mammalian DNA and RNA polymerases, including human mitochondrial RNA polymerase, for ATP over Remdesivir triphosphate, Remdesivir[2] is not a significant inhibitor of these enzymes, which contributes to its overall tolerability and safety profile. Despite this, Remdesivir[3] carries risks for hypersensitivity reactions, including anaphylaxis and other infusion-related reactions, elevated transaminase levels, and potential decreased efficacy when combined with Hydroxy chloroquine or chloroquine. The IUPAC Name of Remdesivir is 2-ethyl butyl (2S)-2-[[[(2R, 3S, 4R, 5R)-5-(4-amino pyrrolo [2, 1-f] [1, 2, 4] triazin-7-yl)-5-cyano-3, 4-dihydroxy oxolan-2-yl] methoxy-phenoxy phosphoryl] amino] propanoate. The Chemical Structure of Remdesivir is

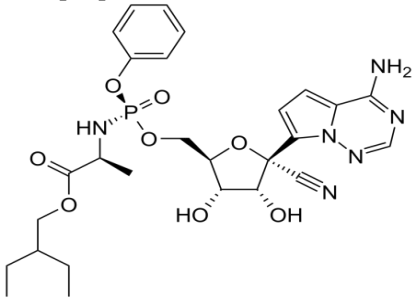

Fig.1. Chemical Structure of Remdesivir

The present study was designed to develop a simple, precise, and rapid analytical RP-HPLC procedure, which can be used for the analysis of assay method for estimation of Remdesivir as there was an only individual method reported for drug. The combination of this drug is not official in any pharmacopoeia; hence no official method is available for the estimation of this drug in alone and their combined dosage forms. Literature survey[24-28] of Remdesivir revealed several methods for detecting these drugs individually but there is some methods are available for their estimation using RP-HPLC. These methods are having some limitations and drawbacks in their previous available methods. The present work describes the development of a simple, precise, accurate and reproducible RP-HPLC method for the Estimation of Remdesivir in bulk form and marketed pharmaceutical dosage forms. The developed method was validated as per ICH guidelines[23] and its updated international convention. The linearity of response, precision, ruggedness and robustness of the described method has been checked.

II. EXPERIMENTAL

Table-1: List of Instrument used

S. No.	Instruments/Equipments/Apparatus
1.	**Waters HPLC** with Empower2 Software with Isocratic with UV-Visible Detector.
2.	**ELICO SL-159** UV – Vis spectrophotometer
3.	Electronic Balance **(SHIMADZU ATY224)**
4.	Ultra Sonicator **(Wensar wuc-2L)**
5.	Thermal Oven
6.	Symmetry RP C_{18}, 5µm, 250mm x 4.6mm i.d.
7.	P^H Analyzer **(ELICO)**
8.	Vacuum filtration kit **(BOROSIL)**

Table-2: List of Chemicals used

S.N.	Name	Specifications		Manufacturer/Supplier
		Purity	Grade	
1.	Doubled distilled water	99.9%	HPLC	Sd fine-Chem ltd; Mumbai
2.	Methanol	99.9%	HPLC	Loba Chem; Mumbai.
3.	Dipotassium hydrogen orthophosphate	96%	L.R.	Sd fine-Chem ltd; Mumbai
4.	Acetonitrile	99.9%	HPLC	Loba Chem; Mumbai.
5.	Potassium dihydrogen orthophosphate	99.9%	L.R.	Sd fine-Chem ltd; Mumbai
6.	Sodium hydroxide	99.9%	L.R.	Sd fine-Chem ltd; Mumbai
7.	Hydrochloric acid	96%	A.R.	Sd fine-Chem ltd; Mumbai
8.	3% Hydrogen Peroxide	96%	A.R.	Sd fine-Chem ltd; Mumbai

Sample & Standard Preparation for the Analysis

25 mg of Remdesivir standard was transferred into 25 ml volumetric flask, dissolved & make up to volume with mobile phase. Further dilution was done by transferring 0.3 ml of the above solution into a 10 ml volumetric flask and make up to volume with mobile phase.

OPTIMIZATION OF CHROMATOGRAPHIC CONDITIONS:

The chromatographic conditions were optimized by different means. (Using different column, different mobile phase, different flow rate, different detection wavelength & different diluents for sample preparation etc.

Table-3: Summary of Process Optimization

Column Used	Mobile Phase	Flow Rate	Wave length	Observation	Result
Develosil ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm	Methanol : Water = 40 : 60	1.0ml/min	248nm	Very Low response	Method rejected
Zorbax ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm	Acetonitrile : Water = 60 : 40	1.0ml/min	248nm	Low response	Method rejected
Inertsil ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm	Acetonitrile: Methanol = 70 : 30	1.0ml/min	248nm	Tailing peaks	Method rejected
Symmetry ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm	Phosphate Buffer : Acetonitrile = 30:70 (pH-4.0)	1.0ml/min	248nm	Resolution was not good	Method rejected
Symmetry ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm	Phosphate Buffer : Methanol = 20:80 (pH-3.8)	1.0ml/min	248nm	Tailing peak	Method rejected
Symmetry ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm	Phosphate Buffer : Acetonitrile = 48:52 (pH-2.8)	1.0ml/min	248nm	Nice peak	Method accepted

Preparation of 0.02M Potassium dihydrogen orthophosphate Solution:

About 2.72172grams of Potassium dihydrogen orthophosphate was weighed and transferred into a 1000ml beaker, dissolved and diluted to 1000ml with HPLC Grade water. The pH was adjusted to 2.80 with diluted orthophosphoric acid Solution.

Preparation of Mobile Phase:

480mL (48%) of above Phosphate buffer solution and 520mL of HPLC Grade Acetonitrile (52%) were mixed well and degassed in ultrasonic water bath for 15 minutes. The resulted solution was filtered[11] through 0.45 µm filter under vacuum filtration.

Method Validation

The method was validated[4] for linearity, accuracy, precision and limit of detection, and limit and quantitation.

System Suitability

In System suitability[5] injecting standard solution and reported USP tailing and plate count values are tabulated in table 1.

Specificity

In this test method placebo, standard and sample solutions were analyzed individually to examine the interference. The below fig. shows that the active ingredient was well separated from blank and their excipients and there was no interference of placebo with the principal peak. Hence the method is specific.

Accuracy: The accuracy[6] of the method was assessed by determination of the recovery of the method at 3 different concentrations (50%, 100% and 150% concentration) by addition of known amount of standard to the placebo. For each concentration three sets were prepared.

Precision: The instrument precision[7] was evaluated by determining the absorbance of the standard solution six times repeatedly. The results are reported in terms of relative standard deviation. The intra-and inter-day variation[20] for the determination was carried out in triplicate for the standard solution.

Linearity

The area of the linearity peak versus different concentrations has been evaluated for Remdesivir, as 10, 25, 50, 75, 100, 125, and 150 percent respectively. Linearity[8] was performed in the range of 1.34-20.1µg/ml of Remdesivir. The correlation coefficient achieved was greater than 0.9991.

Limit of Detection & Quantification: LOD[9] and LOQ were calculated using following equation as per ICH guidelines. LOD = 3.3 × σ/ S and LOQ[10] = 10×σ /S, where σ is the standard deviation of response and S is the slope of the calibration curve.

Robustness

The conditions of the experiment were designed to test the robustness of established system intentionally altered, such as flow rate, mobile phase in organic percentage in all these varied conditions. Robustness[11] results for Remdesivir found to be within the limit and results are tabulated in table 7.

III. RESULTS AND DISCUSSION

Method Development

Selection of Wavelength:

The standard & sample stock solutions were prepared separately by dissolving standard & sample in a solvent in mobile phase diluting with the same solvent.(After optimization of all conditions) for UV analysis. It scanned in the UV spectrum in the range of 200 to 400nm. This has been performed to know the maxima of Remdesivir, so that the same wave number can be utilized in HPLC UV detector for estimating the Remdesivir. While scanning the Remdesivir solution we observed the maxima at 248 nm. The UV spectrum has been recorded on ELICO SL-159 make UV – Vis spectrophotometer model UV-2450. The scanned UV spectrum is attached in the following page,

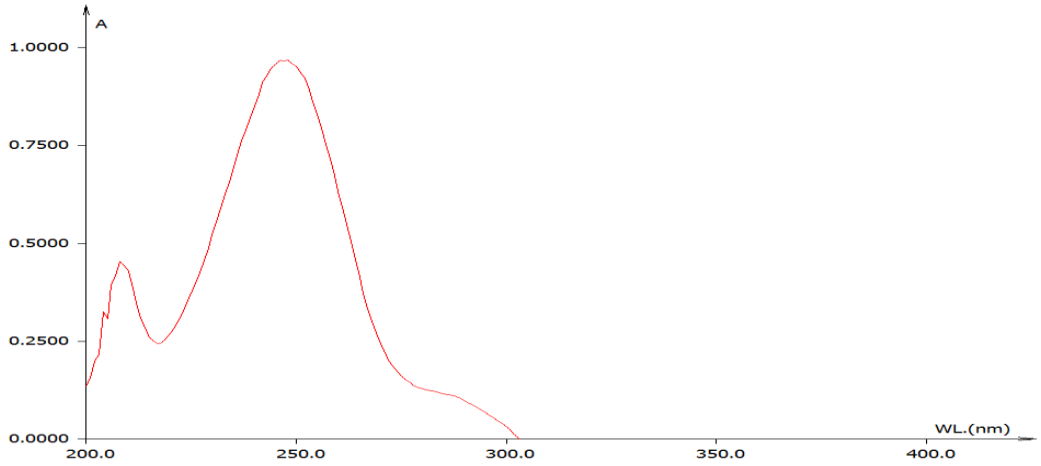

Fig.2. UV Spectrum for Remdesivir

Summary of Optimized Chromatographic Conditions:

The Optimum conditions obtained from experiments can be summarized as below:

Table-4: Summary of Optimised Chromatographic Conditions

Mobile phase	Phosphate Buffer (0.02M): Acetonitrile = 48:52 (pH-2.80)
Column	Symmetry ODS (C_{18}) RP Column, 250 mm x 4.6 mm, 5µm
Column Temperature	Ambient
Detection Wavelength	248 nm
Flow rate	1.0 ml/ min.
Run time	08 min.
Temperature of Auto sampler	Ambient
Diluent	Mobile Phase
Injection Volume	20µl
Mode of Elution	Isocratic

Retention time	3.649 minutes

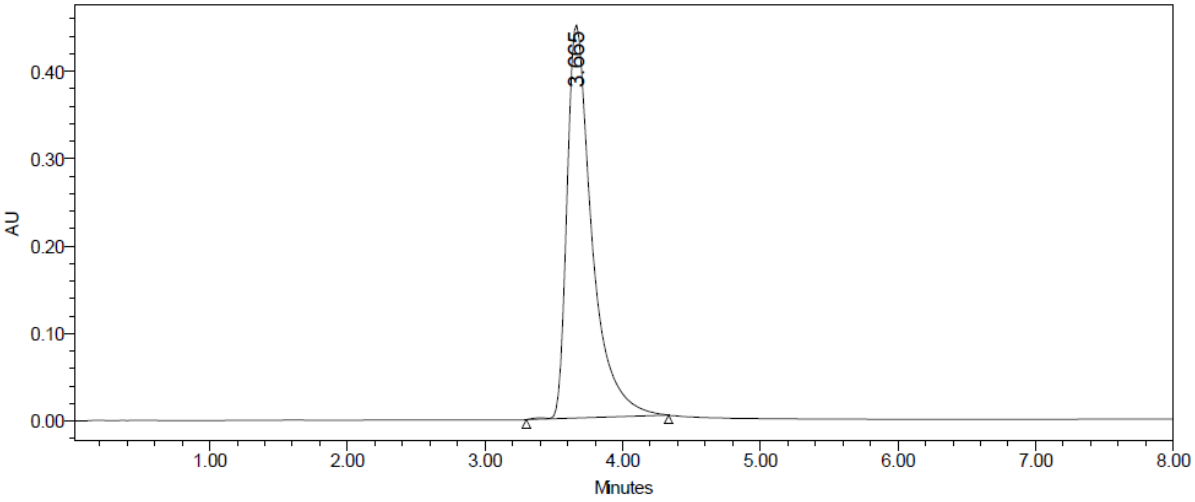

Fig.3. Chromatogram of Remdesivir in Optimized Chromatographic Condition

Validation of Analytical Method

1. Accuracy:

Recovery Study:

To determine the accuracy of the planned technique, recovery studies were distributed by adds completely different amounts (80%, 100%, and 120%) of pure drug of Remdesivir were taken and extra to the pre-analyzed formulation of concentration 30µg/ml. From that proportion recovery values[12] were calculated. The results were shown in table-5.

Table-5: Accuracy Readings

Sample ID	Concentration (µg/ml)		Peak Area	% Recovery of Pure drug	Statistical Analysis
	Amount Added	Amount Found			
S_1 : 80 %	40	40.141	502647	100.352	Mean= 100.3947% S.D. = 0.071319 % R.S.D.= 0.071038
S_2 : 80 %	40	40.191	503214	100.477	
S_3 : 80 %	40	40.142	502656	100.355	
S_4 : 100 %	50	50.044	614215	100.088	Mean= 99.98533% S.D. = 0.183045 % R.S.D.= 0.183071
S_5 : 100 %	50	49.887	612451	99.774	
S_6 : 100 %	50	50.047	614254	100.094	
S_7 : 120 %	60	60.192	728547	100.32	Mean= 100.311% S.D. = 0.408574 % R.S.D.= 0.407308
S_8 : 120 %	60	59.939	725698	99.898	
S_9 : 120 %	60	60.429	731211	100.715	

2. Precision:

2.1. Repeatability

The exactitude[13] of every technique was determined one by one from the height areas & retention times obtained

by actual determination of six replicates of a set quantity of drug. Remdesivir (API). The % relative variance was calculated for Remdesivir square measure bestowed within the table-6.

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Table-6: Repeatability Readings

HPLC Injection Replicates of Remdesivir	Retention Time (Minutes)	Peak Area
Replicate – 1	3.649	5674158
Replicate – 2	3.684	5654715
Replicate – 3	3.687	5665841
Replicate – 4	3.688	5654578
Replicate – 5	3.688	5652284
Replicate – 6	3.687	5641487
Average		**5657177**
Standard Deviation		**11369.72**
% RSD		**0.200979**

2.2. Intermediate Precision:

2.2.1. Intra-assay & inter-assay:

The intra & inter day variation[14] of the method was carried out & the high values of mean assay & low values of standard deviation & % RSD (% RSD < 2%) within a day & day to day variations for Remdesivir revealed that the proposed method is precise.

Table-7: Results of intra-assay & inter-assay

Conc. of Remdesivir (API) (µg/ml)	Observed Conc. of Remdesivir (µg/ml) by the proposed method			
	Intra-Day		Inter-Day	
	Mean (n=6)	% RSD	Mean (n=6)	% RSD
40	40.05	1.09	39.89	1.08
50	50.08	0.95	49.54	0.76
60	60.09	0.97	59.86	0.94

3. Linearity & Range:

The calibration curve showed good linearity in the range of 0-70µg/ml, for Remdesivir (API) with correlation coefficient (r^2) of 0.999 (Fig-4). A typical calibration curve has the regression equation[15] of y = 11266.x + 50416 for Remdesivir.

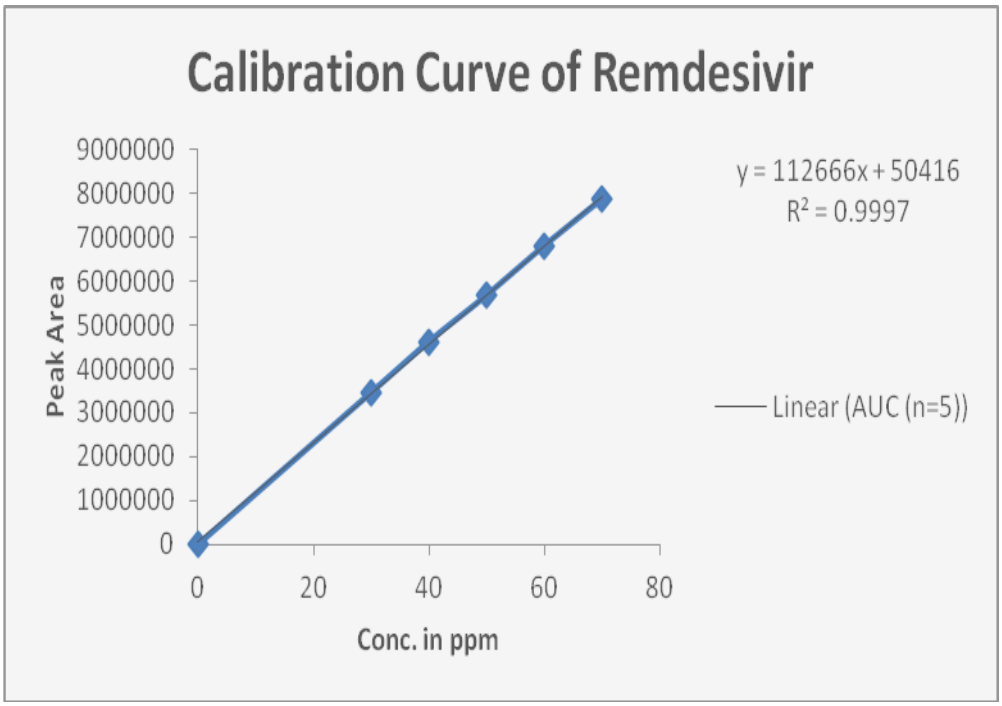

Fig.3. Calibration Curve of Remdesivir (API)

Table-8: Linearity Results

CONC.(µg/ml)	MEAN AUC (n=6)
0	0
30	3465974
40	4626478
50	5682284
60	6815478
70	7878721

4. Method Robustness:

Influence of small changes in chromatographic conditions[16] such as change in flow rate (± 0.1ml/min), Temperature (±2^{0}C), Wavelength of detection (±2nm) & Acetonitrile content in mobile part (±2%) studied to work out the strength of the tactic also are in favour of (Table-9, nada RSD < 2%) the developed RP-HPLC technique for the analysis of Remdesivir (API).

Table-9: Result of Method Robustness Test

Change in parameter	% RSD
Flow (1.1 ml/min)	0.56
Flow (0.9 ml/min)	0.87
Temperature (27^{0}C)	0.72
Temperature (23^{0}C)	0.53
Wavelength of Detection (257 nm)	0.61
Wavelength of detection (253 nm)	0.96

5. LOD & LOQ:

The Minimum concentration level at which the analyte can be reliable detected (LOD) & quantified (LOQ) were found to be 0.09 & 0.27 µg/ml respectively.

6. System Suitability Parameter:

System quality testing is associate degree integral a part of several analytical procedures[17]. The tests square measure supported the idea that the instrumentation, physics, associate degree analytical operations and samples to be analyzed represent an integral system that may be evaluated intrinsically. Following system quality check parameters were established. The info square measure shown in Table-10.

Table-10: Knowledge of System quality Parameter

S.No.	Parameter	Limit	Result
1	Resolution	Rs > 2	8.54
2	Asymmetry	T ≤ 2	Remdesivir =0.98
3	Theoretical plate	N > 2000	Remdesivir =4782

4	Tailing Factor	T<2	Remdesivir =1.49

7. Estimation of Remdesivir in Pharmaceutical Dosage Form

Twenty pharmaceutical dosage forms were taken and the I.P. method was followed to work out the typical weight. On top of weighed tablets were finally pulverized[18] and triturated well. A amount of powder cherish twenty five mg of medicine were transferred to twenty five cc meter flask, build and resolution was sonicated for quarter-hour, there once volume was created up to twenty five cc with same solvent. Then ten cc of the on top of resolution was diluted to a hundred cc with mobile part. The answer was filtered through a membrane filter (0.45 µm) and sonicated to remove. The answer ready was injected in 5 replicates into the HPLC system and therefore the observations were recorded.

A duplicate injection of the quality resolution[19] was conjointly injected into the HPLC system[20] and therefore the peak areas were recorded. The info square measure shown in Table-11.

ASSAY:

Assay % =

$$\frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{WT} \times \frac{P}{100} \times \text{Avg. Wt} = \text{mg/tab}$$

Where:

AT = Peak space of drug obtained with check preparation
AS = Peak space of drug obtained with normal preparation
WS = Weight of operating normal taken in mg
WT = Weight of sample taken in mg
DS = Dilution of normal resolution[21]
DT = Dilution of sample resolution
P = proportion purity of operating normal

Table-11: Recovery Data for estimation Remdesivir

Brand Name of Remdesivir	Labelled amount of Drug (mg)	Mean (± SD) amount (mg) found by the proposed method (n=6)	Assay % (± SD)
Covifor Vial (100mg) (Hetero)	100mg	99.798 (± 0.698)	99.698 (± 0.859)

Result & Discussion: The amount of drug in Remdesivir Vial was found to be 99.798 (± 0.698) mg/tab for Remdesivir & % assay[22] was 99.698 %.

Stability Studies

Results of Degradation Studies:

The results of the stress studies indicated the Specificity[23] of the method that has been developed. Remdesivir was stable in photolytic and peroxide stress conditions. The results of forced degradation studies are given in the following table-12.

Table-12: Results of Forced Degradation Studies of Remdesivir API

Stress Condition	Time	Assay of active substance	Assay of degraded products	Mass Balance (%)
Acid Hydrolysis (0.1 M HCl)	24Hrs.	98.76	1.24	100.0
Basic Hydrolysis (0.1 M NaOH)	24Hrs.	98.63	1.37	100.0
Thermal Degradation (50 ^{0}C)	24Hrs.	93.98	6.02	100.0

UV (248nm)	24Hrs.	98.84	1.16	100.0
3 % Hydrogen Peroxide	24Hrs.	94.61	5.39	100.0

IV. SUMMARY AND CONCLUSION

We present in this article simple, selective, validated and well-defined stability that shows isocratic RP-HPLC methodology for the quantitative determination of Remdesivir. All the products of degradation formed during the stress conditions and the active pharma ingredient were well separated and peaks were well resolved from each other and separate with an appropriate retention time indicating that the proposed method to be fast, simple, feasible and affordable in assay condition. Therefore the developed method during stability tests, it can be used for routine analysis of production standards and to verify the quality of drug standards during stability studies. Thus, the objective of project work to develop and validate suitable method for the determination of Remdesivir in API form and marketed pharmaceutical dosage form was achieved. Developed and validated RP-HPLC for Remdesivir were found to be simple, rapid, specific, sensitive, precise and cost effective. This analytical method can also be applied for assay and related substances stability testing studies for the respective drug.

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