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Quantitative Analysis of Drug from Bulk as Well as Formulation

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Abstract: ***A simple, precise, accurate method was developed for the estimation of molnupiravir by RP HPLC. Chromatographic conditions used are stationary phase Hemochrom C18 (4.6mm x 250mm x 5µm), mobile phase methanol for 5 minutes then 0.1% orthophosphoric acid and methanol in a ratio of 50:50 from 5 – 20 min. The flow rate was maintained at 1.0 ml/min, the detection wavelength was 235 nm, column temperature was set to 30° C and diluent were water and methanol (50:50) was finalized as an optimized method. System suitability parameters were studied by injecting the standard six times and the results were well under acceptance limits. Theretention time for molnupiravir was 10 min. The method was validated for linearity, accuracy, precision, specificity, the limit of quantification, detection, and robustness. The limit of detection and limit of quantificationwas found to be 0.5 µg/ml and 1.5 µg/ml respectively and recovery of molnupiravir from molnupiravir capsule was found 98.72 %. The proposed method was successfully applied for the quantitative determination of molnupiravir capsule formulation.***

Keywords: Molnupiravir, RP-HPLC, Method Development, Validation, Forced Degradation, Peak purity index.

I. INTRODUCTION

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a new coronavirus (CoV), which is the cause of the COVID- 19 pandemic, has grown to be a significant concern to public health. More than 115 millionindividuals will have contracted the disease by March 8th, 2021, and sadly, approximately 2.5 million will have perished [1]. Molnupiravir, an antiviral medication with two brand names (MK-4482 and EIDD-2801) that is usedto treat influenza, is one of the useful medications in this regard [2]. This prodrug, which is being developed by Merckfirm as a novel oral anti-viral medication for the treatment of COVID-19, has a nucleoside scaffold of N4-hydroxycytidine [3],[4]. It was initially created at Emory University with the assistance of the university's drug discovery company. Molnupiravir efficacy in preventing viral transmission and inhibiting SARS-CoV 22 was shown by testing the medication on various animal species [5],[6],[7],[8],[9]. This medication, which is based on an oral antiviral ribonucleoside analog, is known as a 5′-isobutyrate prodrug of the direct-acting antiviral ribonucleoside analog EIDD-1931 or - D N4-hydroxy cytidine. EIDD-1931 is produced in the plasma when molnupiravir cleaves[10],[11]. The active anti-viral drug, EIDD-1931 5′-triphosphate, is phosphorylated intracellularly by host kinases. Molnupiravir IUPAC name is ((2R,3S,4R,5R)Its chemical name is C13H19N3O7, and its molecular formula is4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl)methyl isobutyrate. Molnupiravir has a 329.31 molecular weight [12]

A review of the literature found that molnupiravir pharmacokinetics studies were done in people. The effectiveness and safety of molnupiravir and numerous other drugs were also compared in controlled field research. Molnupiravir can be separated using a liquid chromatographic process that has been verified [13],[14],15].

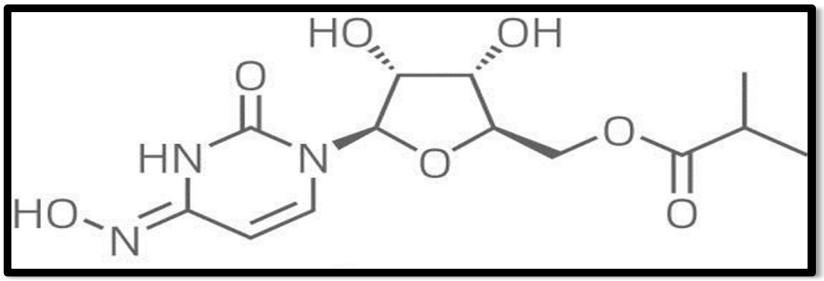

Fig.1 Chemical structure of Molnupiravir

Here, efforts were undertaken to establish a reverse phase chromatographic method (RP-HPLC) that was straightforward, precise, quick, accurate, and cost-effective for estimating molnupiravir in bulk and formulation.Additionally, techniques like uv-vis techniques are insufficient to calculate an exact amount of API. The study ofthis API similarly reveals insufficient resolution due to poor reproducibility [16],[17],[18]. Keeping this in mind the RP-HPLC method was developed and validated for quantification. Therefore, in the present investigation, a novel HPLC method was developed and validated for the quantification of this API and degradation studies under ICH guidelines [19].

II. MATERIAL AND METHODS

A. *Instrumentation*

HPLC instrument used was of Shimadzu iprominence with PDA detector. The software used is Lc lab solutions. UV – VIS spectrophotometer PG instrument T 60 with special bandwidth of 2nm and 10 nm and matched quartz was used for measuring absorbance for molnupiravir [20].

B. *Chemicals*

The molnupiravir reference standard was obtained from the capsule of the brand Moluzen (Xenon pharma) of 200mg was obtained from Shuban Pharmaceutical Pvt Ltd, Bhiwandi (India), and also molnupiravir standard was supplied by Shuban Pharmaceutical Pvt Ltd, Bhiwandi (India).

C. *Chromatographic conditions*

Glasswares in each procedure were soaked overnight in a hot air oven. Hemochrom C18 (4.6mm x 250mm x 5 µm) was used at 30· C. Gradient elution was performed with 0-5 min (100% of 0.1% OPA), and 5-20 min (0.1% OPA: methanol in ratio of 50:50).

D. *Preparation of standard solutions*

Accurately weigh 50 mg std molnupiravir in a 50 ml volumetric flask and sonicated for 10 minutes. Flask was made up to the mark by water (stock sample solution). Take 1ml from stock , add in 100 ml flask. Add some amount of diluent (water and methanol in the ratio of 50:50). Sonicated it for 10 minutes. Flask was made up tothe mark by diluent.

E. *Preparation of sample solution*

Ten capsules of (Moluzen, 200 mg) have been weighed and mixed with the powder. Accurately weighed tablet powder containing 60 mg of molnupiravir was transferred to a 50 ml calibrated flask and dissolved in deionized water. The content was shaken for 30 min. The volume was completed with deionized water to get the concentration of 1000 µg mL-1 (stock sample solution). Then further sample solution was made to get 10 µg/mLsolution by adding 1 ml from stock in a 100 ml flask and then diluting with diluent in the ratio of 50:50 (water: methanol). The final solution was filtered using a Whatman filter paper (No. 42) [21].

III. METHOD VALIDATION

The proposed method was validated as per ICH Q2 (R1) guidelines for specificity, linearity, range, accuracy, precision, and robustness.

A. *Specificity*

Specificity, also known as selectivity, is the ability of an analytical method to measure the analyte of interest accurately in the presence of potential interfering substances. It ensures that the method can distinguish and quantifythe target analyte without being affected by other components in the sample matrix. To assess specificityforced Degradation Studies is carried out Subject the analyte to various stress conditions (e.g., heat, light, acid, base) to assess if the method can accurately detect and quantify degradation products.

B. *Linearity*

Linearity refers to the ability of the analytical method to produce results that are directly proportional to the concentration of the analyte in the sample over a specific range. A linear relationship implies that the method's response is consistent and predictable across a range of concentrations.

C. Range

In High-Performance Liquid Chromatography (HPLC) method validation, the term "range" refers to the concentration interval over which the analytical method is expected to provide accurate and precise results. Determining the appropriate range for your HPLC method is crucial for ensuring that the method can effectively quantify the analyte of interest within the desired concentration levels.

D. Accuracy

To assess the accuracy of the proposed method, recovery studies were carried out at three different levels i.e. 50 %, 75%, 100%, and 150%. To the pre-analyzed sample solution, a known amount of standard drug solution wasadded at three different levels, absorbance was recorded. The % recovery was calculated by using the formula

% recovery= A- B / C

Where A = total amount of drug estimated, B= amount of drug found on pre analyzed basis, C= amount of puredrug added

E. Precision

Precision assessment in HPLC method validation provides insights into the method's ability to generate consistentand reliable results, which is crucial for obtaining accurate data in analytical work. It helps ensure that the methodis suitable for its intended purpose and that the variability in results is within acceptable limits.

F. Robustness

Small deliberate changes in a method like flow rate, mobile phase ratio, and temperature are made but there wereno recognized changes in the result, and are within the range as per ICH guidelines [22],[23],[24].

IV. RESULTS

A. Selection of detection wavelength

The UV spectra of molnupiravir in methanol in the region between 200 to 400 nm are shown in Fig 2. It shows that at 235 nm molnuiravir has maximum absorbance. Hence max of molnupiravir in the mobile phase was selected as the optimum detection wavelength for quantification of molnupiravir.

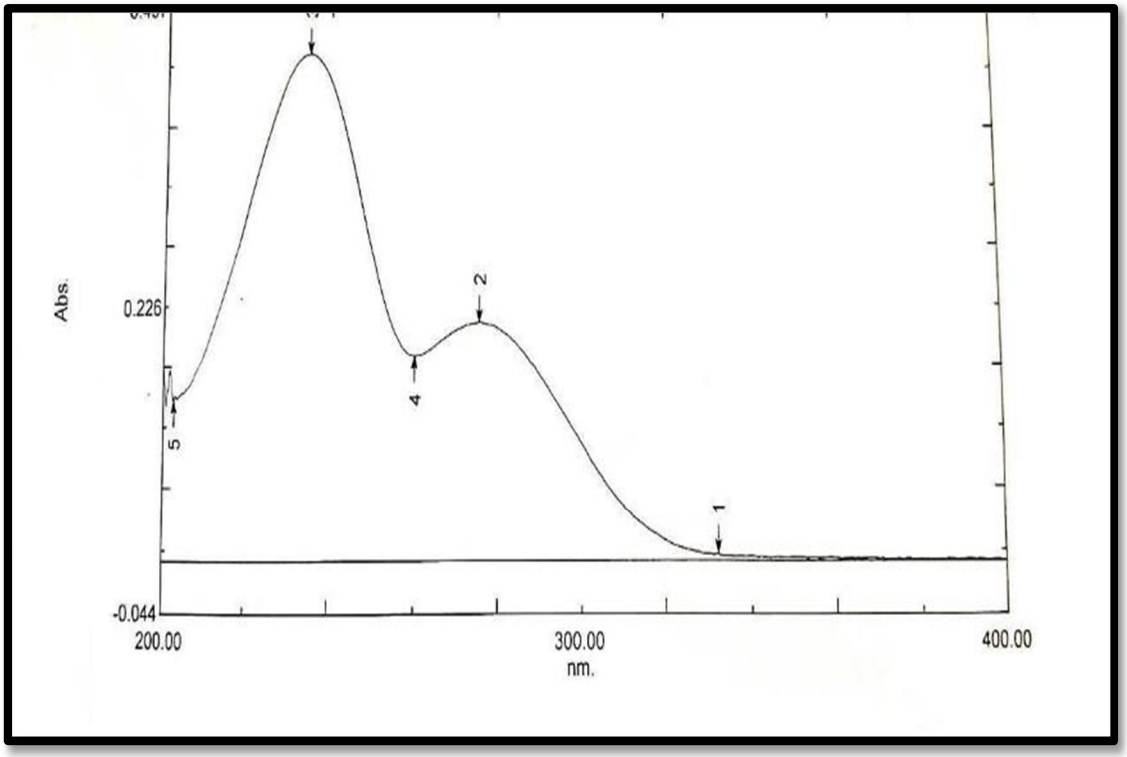

Fig. 2 Absorbance spectrum of molnupiravir in methanol

B. Optimized chromatographic conditions

1) Column: Hemochrom C18 (4.6mm x 250mm x 5µm)
2) Mobile phase: 0-5 min (100% of 0.1 % OPA), 5-20 min (OPA and methanol in ratio of 50:50)(iii)
3) Flow rate: 1.0ml/min
4) Detector: PDA detector
5) Temperature: 30° C
6) Injection volume: 10µL [25]

C. Robustness, limit of detection, and limit of quantification

Robustness was done bychanging parameters like mobile phase ratio, and flow rate. LOD and LOQ are calculatedby the S/N ratio.

D. System suitability

The Standard solution of molnupiravir working standard was prepared as per procedure and was injected 5 timesinto the HPLC system. The system suitability parameters were evaluated from a standard chromatogram obtainedby calculating % RSD of retention time, tailing factor, theoretical plates, and peak areas from the above replicateinjection are within range and results were shown in Table 1.

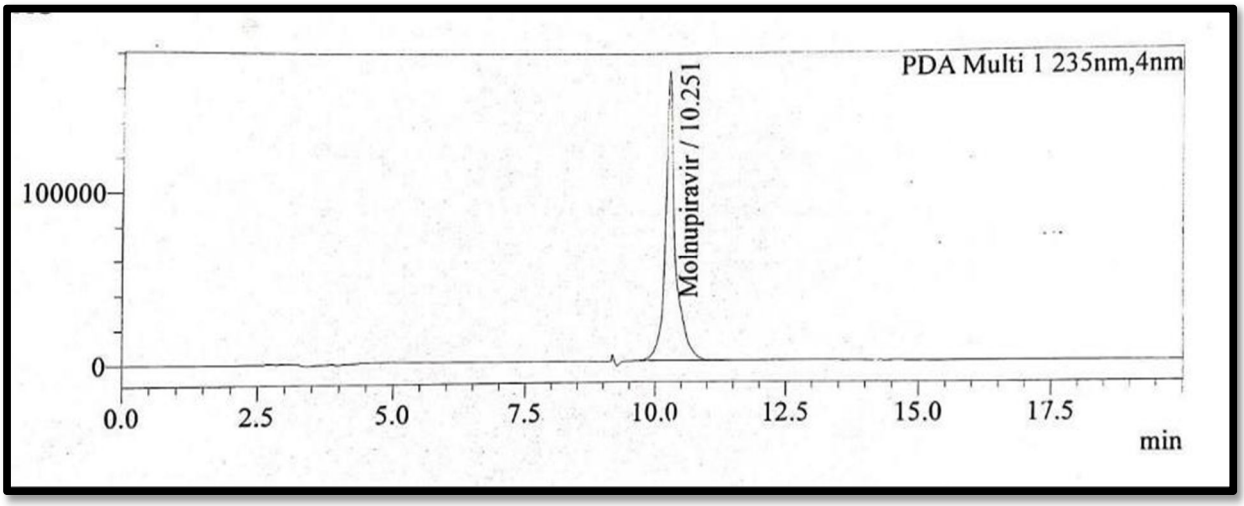

Fig. 3 Optimized chromatographic conditions

Table. 1 System suitability data

Sr.no	Peak name	Area	Retentiontime	USP platecount	USP tailing
1	Molnupiravir	235033	10.0	25544	0.97
2	Molnupiravir	235335	10.0	25458	0.97
3	Molnupiravir	236130	9.9	25802	0.98
4	Molnupiravir	235469	10.0	26020	0.99
5	Molnupiravir	235975	10.0	26159	0.99
6	Molnupiravir	236129	10.0	25562	0.97
	Mean	235678.5	10.0		
	SD	463.3071	0.017		
	%RSD	0.196	0.167		
	Limit	NMT 2.0%	MMT 1.0 %		

E. Linearity

The method can elicit test result that is directly proportional to analyte concentration within a given range. It is generally reported as the variance of the slope or regression line. The appropriate volume of standard stock solution was transferred to a volumetric flask of 100 ml capacity. The volume was adjusted to the mark with diluent to give a solution containing 10, 20, 40, 80, 100, 200 ppm. The slope, Y-intercept, and correlation coefficient were calculated. The regression line relating to the standard concentration of the drug using regressionanalysis was calculated. The calibration curve was linear in the standard range and an equation of regression analysis was obtained.

Table. 2 Linearity data of molnupiravir

Concentration (µg/ml)	InjectionNo	Area	Average
10	1	225269	225126
	2	224983	
20	1	473717	464075
	2	464433	
40	1	918736	918761
	2	918786	
80	1	1918970	1918750
	2	1918530	
100	1	2369877	2368810
	2	2367742	
200	1	2732495	2732328
	2	2732161	

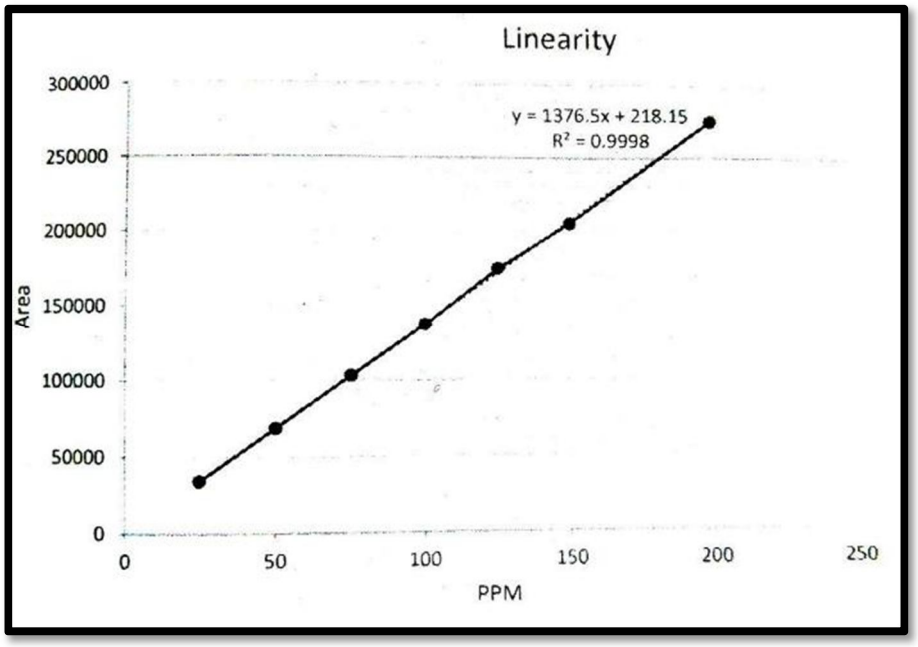

Fig. 4 Calibration curve of molnupiravir

F. Range

The linearity of an analytical procedure is its ability (within a given range) to obtain test results that are directly proportional to the concentration (amount) of analyte in the sample. The conc. The range is between 10 to 200 µg/ml.

G. LOD and LOQ

LOD and LOQ were calculated from the formula 3.3 x (σ/S) and 10 x (σ/S) respectively where σ is the standard deviation of intercept and S is the mean of slope. The LOD and LOQ can be determined by S/N.
The value for LOD should be 0.5 µg/ml and 1.5 µg/ml.

H. Precision

1) System precison: Six working standard solutions of 10 ppm are injected and % amount found was calculated and the % RSD wasfound to be 0.196

Table. 3 System precision

Injection No.	Area	Limit
1	235033	NMT 2.0%
2	235335	
3	236130	
4	235469	
5	235975	
6	236129	
Mean	235678.5	
SD	463.3071	
%RSD	0.196	
Limit	NMT 2.0%	

2) Method precision: Six working standards and a sample of 10 ppm were injected into the HPLC system and the % amount found wascalculated and the % RSD was found to be 0.312.

Table. 4 Method precision

Sample no	% Assay	Limit
1	98.57	NMT 2.0 %
2	99.32	
3	98.98	
4	98.97	
5	99.41	
6	98.85	
mean	99.01	
SD	0.3090	
% RSD	0.312	

3) Interday Precision: Six working standards and a sample of 10 ppm were injected on the next day of preparation of samples and the % amount found was calculated and the % RSD was found to be within specified limits of acceptance criteria:the % RSD for all six standard injections should be not more than 2.0%.

Table. 5 Interday precision

Sample No	Day 1	Day 2	Limit
1	98.57	99.01	NMT 2.0 %
2	99.32	99.64	
3	98.98	98.96	
4	98.97	99.23	
5	99.41	99.46	
6	98.85	99.83	
Mean	99.01	99.35	
SD	0.3090	0.3488	
% RSD	0.312	0.251	

I. Accuracy

Four concentrations of 50%, 75%, 100%, and 150% were injected and % recovery was calculated as 98.72%.

Table. 6 Accuracy and recovery

% level	Amount added (µg/ml)	Amount recovered(mg)	% amount recovered	% recovered	Mean % recovered
50	25	24.6	49.24	98.13	
75	37.5	37.4	74.78	99.71	
100	50	49.4	98.89	98.89	
150	75	73.7	147.25	98.17	98.72%

J. Assay of marketed formulation

Standard and sample solutions were injected after a 0.45 um syringe filter into the system and the drug present insamples was calculated using formula [26[,[27],[28].

Table. 7 Assay of molnupiravir

SampleNo	Weight of standard(mg)	Sample weight (equivalent to 50mg)	The mean area of the standard at 235 nm	ea of the sample at 235nm	% Assay
1	50 mg		235619	230106	98.57
2				231863	99.32
3				231079	98.98
4				231060	98.97
5				232087	99.41
6				230771	98.85
			Mean	231161	99.01
Average Weight	50.5 mg	60.1 mg	SD	725.57	0.309
Limit	NMT 2.0%		% RSD	0.313	0.312

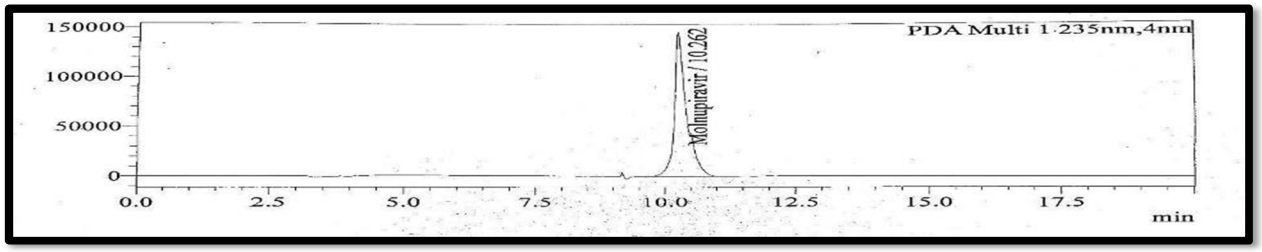

Fig. 5 Assay chromatogram of molnupiravir

V. FORCED DEGRADATION STUDIES

Degradation studies were performed with formulation and degraded samples were injected. The assay of injectedsamples was calculated and all the samples were passed the limit of degradation. Degradation sample preparation are as given below.

A. Acid degradation studies

To the 1ml of stock sample solution, 1ml of 0.1 N HCL was added separately in a 100 ml flask. The solution waskept at 60° C for 4 hrs. for the HPLC study, the resultant solution was diluted with diluent to obtain 10 µg/ml, and10 µl was injected into the system after filtering through a syringe filter, and a chromatogram was recorded to assess the stability of the sample.

B. Alkali degradation studies

To the 1ml of stock sample solution, 1ml of 0.01 N NaOH was added separately in a 100 ml flask. The solution was kept at room temperature for 2 mins. For the HPLC study, the resultant solution was diluted with diluent to obtain 10 µg/ml, and 10 µl was injected into the system after filtering through a syringe filter, and chromatogramswere recorded to assess the stability of the sample.

C. Oxidative degradation studies

To the 1ml of stock sample solution, 1ml of 5 % H_2O_2 was added separately in a 100 ml flask. The solution waskept at 60° C for 4 hrs. For the HPLC study, the resultant solution was diluted with diluent to obtain 10 µg/ml, and10 µl was injected into the system after filtering through a syringe filter, and a chromatogram was recorded to assess the stability of the sample.

D. Water degradation studies

To the 1ml of stock sample solution, 1ml of water was added separately in a 100 ml flask. The solution was keptat 60° C for 4 hrs. For the HPLC study, the resultant solution was diluted with diluent to obtain 10 µg/ml, and 10 µl was injected into the system after filtering through a syringe filter, and a chromatogram was recorded to assessthe stability of the sample [29].

Table. 8 Degradation data of molnupiravir

Sr no	Degradation type	Conditions	Duration	Retention time on degradation products (min)	% residual Drug(%)	Observedpeak purity	Acceptance limit of peak purity
1	Acid degradation	1ml of 0.1NHCL at 60° C	4 hrs	10.2	94.21	100.00	NLT 99 %
2	Alkaline degradation	1ml of 0.01NNaOH at room temperature	2 min	10.3	96.94	100.00	
3	H_2O_2 degradation	1 ml of 5% H_2O_2 at 60° C	4 hrs	10.2	97.63	100.00	
4	Water degradation	1ml of H_2O at 60° C	4 hrs	10.2	100.00	100.00	

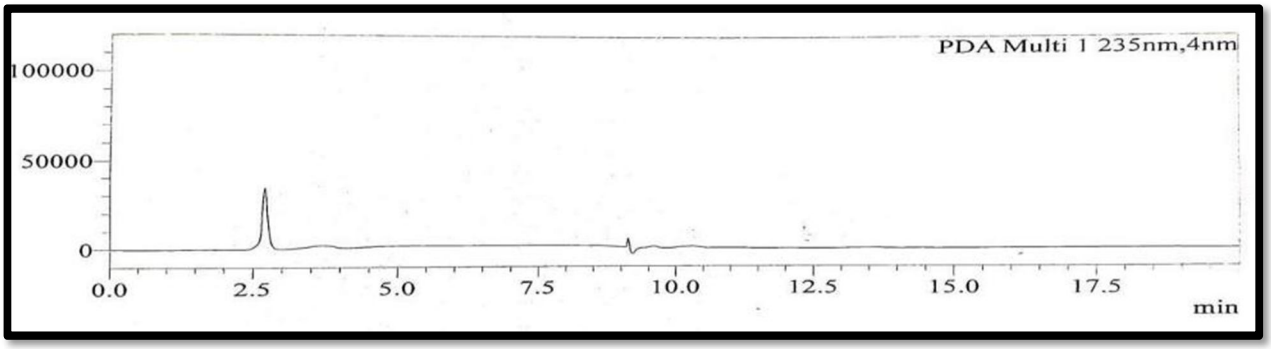

Fig. 6 Blank chromatogram

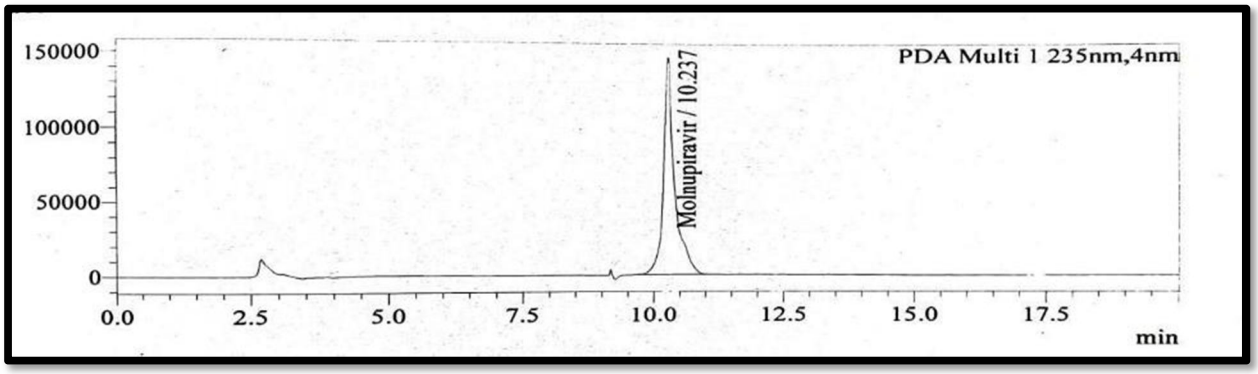

Fig. 7 Chromatogram of acid degradation

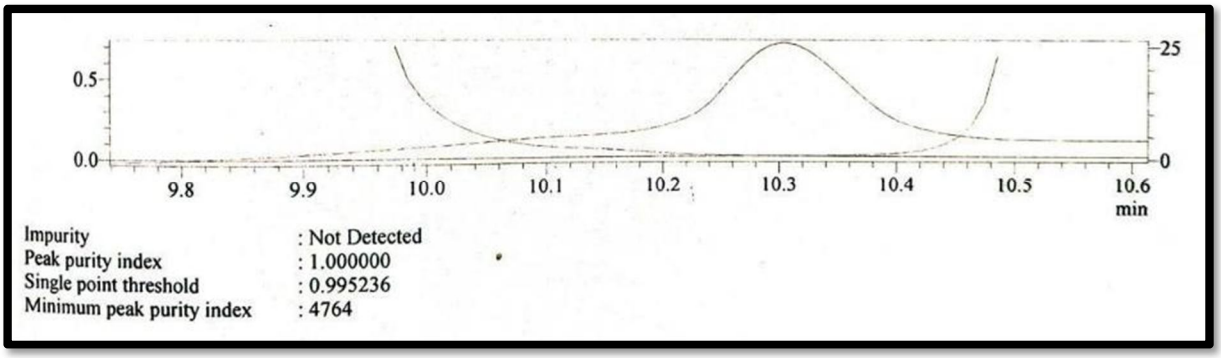

Fig. 7A Peak purity index in acidic degradation

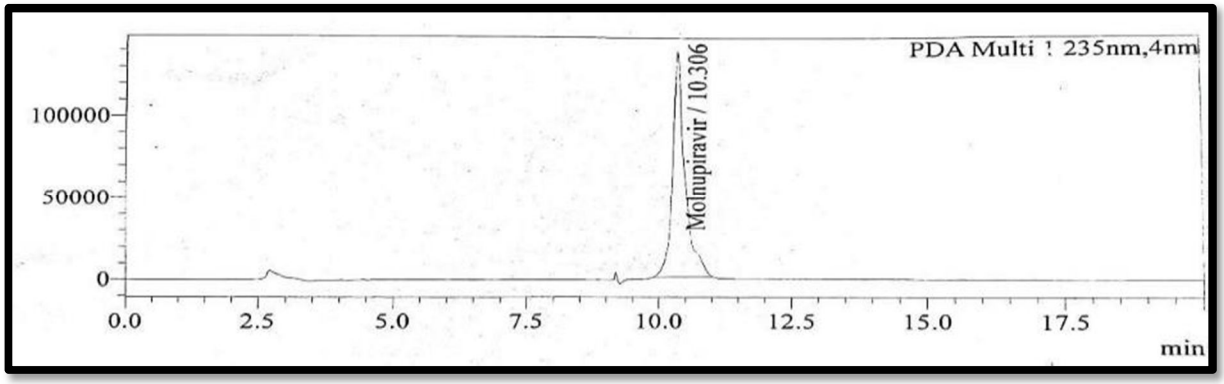

Fig. 8 Chromatogram of alkaline degradation

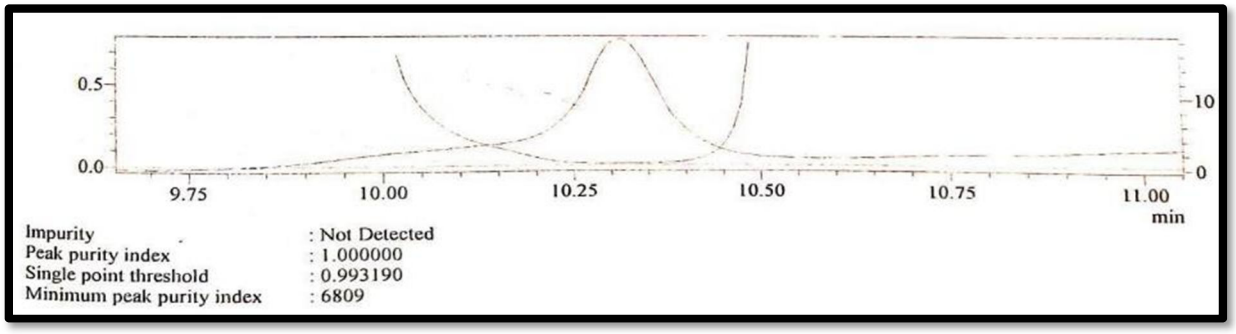

Fig. 8A Peak purity index in alkaline degradation

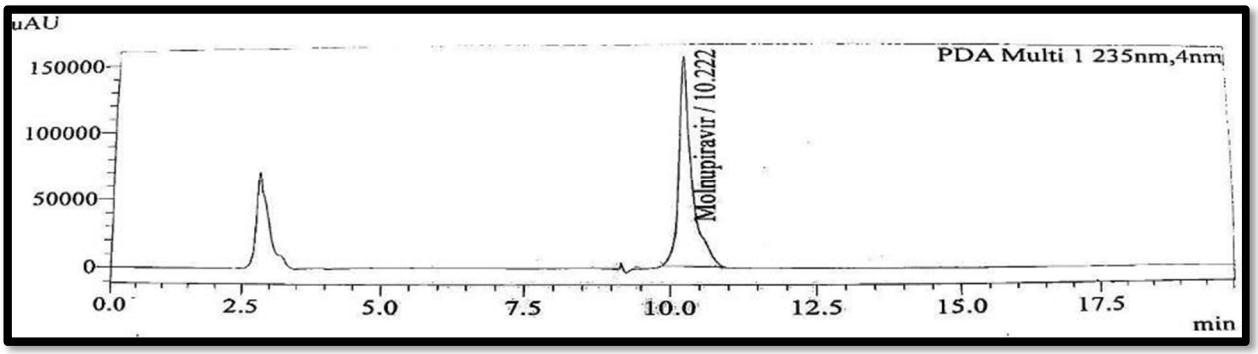

Fig 9 Chromatogram of hydrogen peroxide degradation

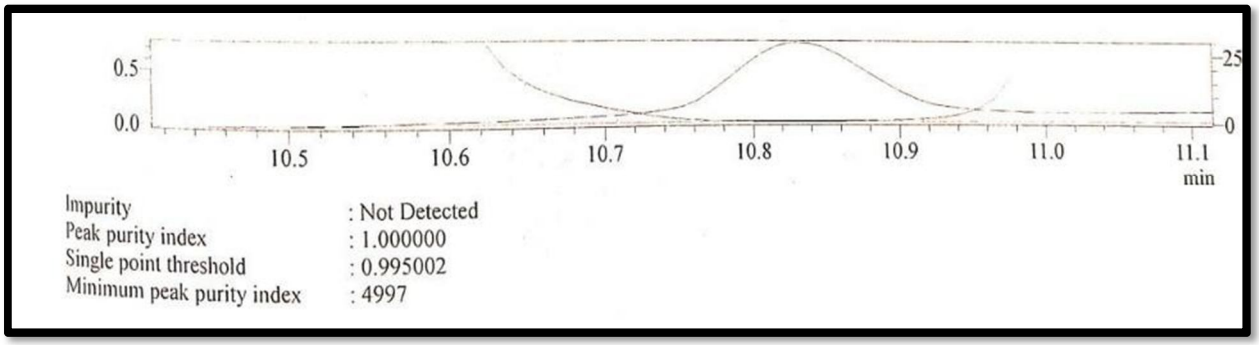

Fig. 9 A. Peak purity index hydrogen peroxide degradation

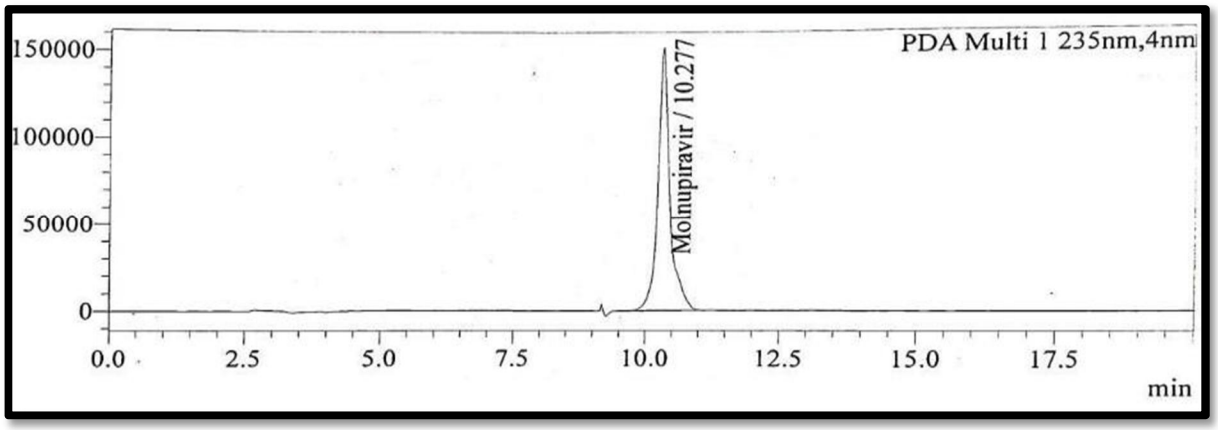

Fig. 10 Chromatogram of hydrolytic degradation

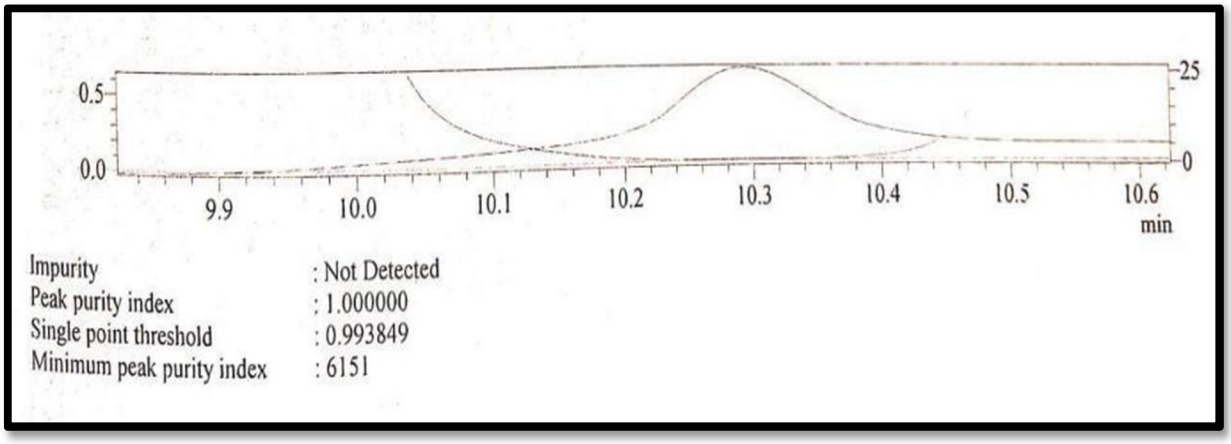

Fig 10A. Peak purity index in hydrolytic degradation

VI. DISCUSSION

Regarding the p^H adjustment in the mobile phase for acid and base degradation studies have movement in the retention time of the drugs. But due to the addition of OPA, there will be no change in retention time. The summarized data is shown in Table 9.

Table 9. Summarized data

Parameters	Molnupiravir	Limit
Linearity: Range (µg/ml)	10 – 200 µg/ml	R < 1
Regression coefficient	0.9998	
Slope (m)	1376.5	
Intercept (c)	218.15	
Regression equation(y=mx+c)	Y= 1376.5 x +218.15	
Assay (% mean assay)	99.01 %	98 – 102 %
Specificity	Specific	No interference of anypeak
System precision % RSD	0.196	NMT 2.0 %
Method precision % RSD	0.312	
Interday precision % RSD	0.251	
Accuracy & recovery %	98.72 %	98 – 102 &
LOD	0.5 (µg/ml)	NMT 3
LOQ	1.5 (µg/ml)	NMT 10
Robustness Wavelength (± 2 nm)	0.689	% RSD NMT 2.0 %
Mobile Phase (± 2ml)	0.292	
Flow rate (±0.2ml/min)	0.585	

VII. CONCLUSION

Chromatographic conditions used are stationary phase Hemochrom C18 (4.6mm x 250mm x 5µm), mobile phase for 0-5 min 100% orthophosphoric acid, for 5- 20 min 0.1% orthrophosphoric acid and methanol in ratio of 50:50 and flow rate were maintained at 1.0 ml/min, detection wavelength was 235 nm, column temperature was set to 30° C and diluent methanol and water in a ratio of 50:50 were finalized as an optimized method. Systemsuitability parameters were studied by injecting the standard six times and the results were all under the acceptancecriteria. A linearity studywas carried out between 10–200, R^2 value was found to be 0.9998. precision was foundto be 0.312 for the method and 251 for interday precision. LOD and LOQ were found to be 0.5 and
1.5 respectively. By using the above method assay of the marketed formulation was carried out. Degradation studies of molnupiravir were done, in all conditions purity threshold was more than the purity angle and within the acceptable range.

VIII. ACKNOWLEDGMENT

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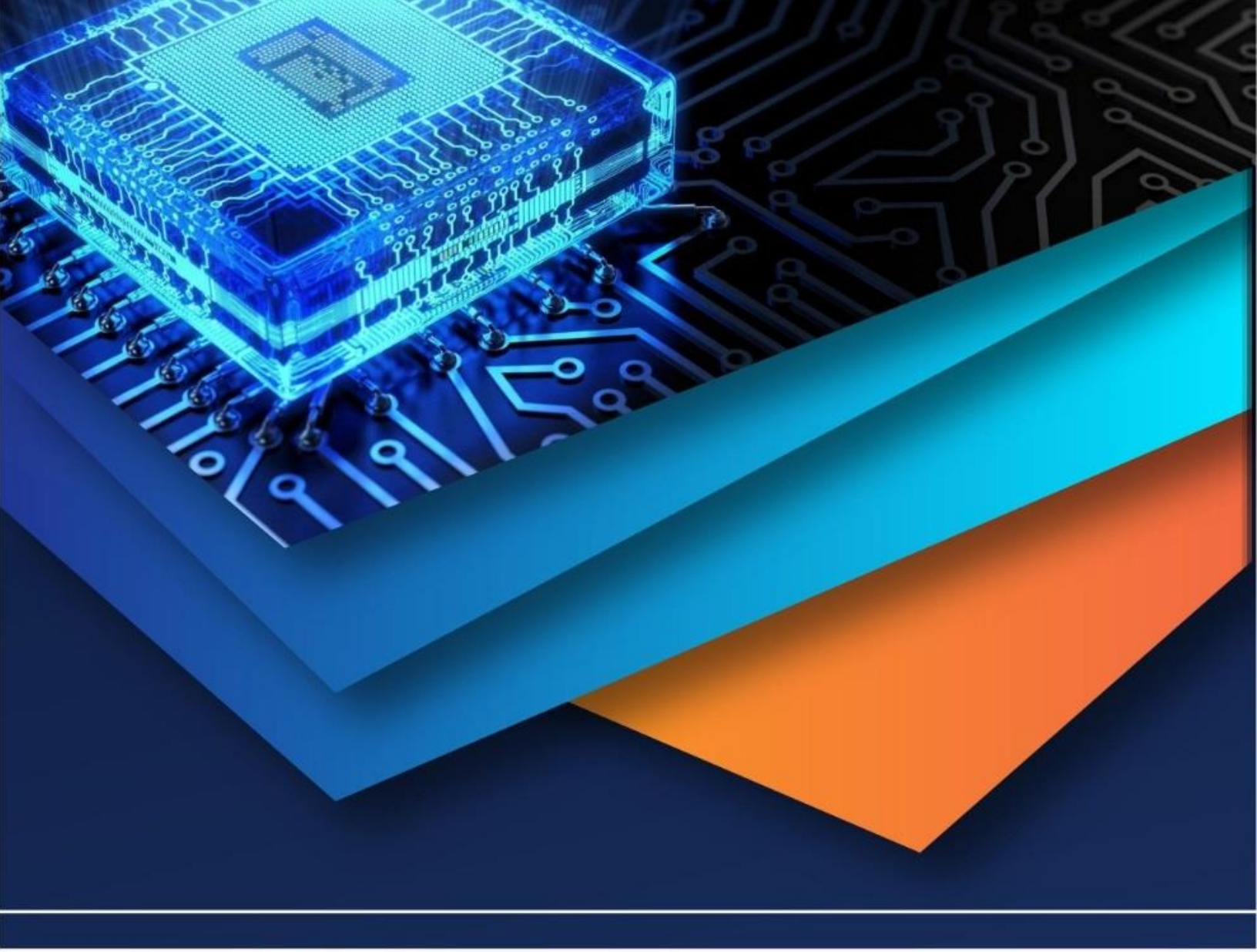

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