



DEVELOPMENT AND VALIDATION OF MOLNUPIRAVIR IN PHARMACEUTICAL DOSAGE FORM

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Abstract:

The present study was focused to develop a simple, precise, accurate and cost effective RP-HPLC method for estimation of Molnupiravir in Pharmaceutical dosage form. The chromatographic method was carried out using Kromasil 100-5-C18 (150 mm x 4.6 mm) 5 μ column with mobile phase Buffer solution (0.1% Orthophosphoric acid): Acetonitrile in ratio of 85:15 % v/v. The flow rate was set 1.0 ml/min with 10 μ L injection volume. Total run time 10 min. Detection was carried out at the wavelength of 235 nm. The detector response was linear in the concentration range of 50 – 150 μ g/ml with a correlation coefficient of 0.999. . The developed analytical method was validated according to the ICH guideline. The developed method is successfully applied for estimation of Molnupiravir in Pharmaceutical dosage form

Keywords: Molnupiravir, RP-HPLC, Method Development, Validation.

1. Introduction to Corona Virus¹⁻⁵

1.1 SARS-CoV-2/COVID-19

- 2019 Novel Coronavirus (SARS-CoV-2), causing coronavirus disease 2019 (COVID-19), is a virus identified as the cause of an outbreak of respiratory illness first detected in Wuhan, China.
- Initially, the patients were believed to have contracted the virus from seafood/animal markets which suggested animal-to-human spread.
- The growing number of patients however, suggest that human-to-human transmission is actively occurring.

Signs and Symptoms:

- Fever, Tiredness, Cough, Loss of taste or smell, Difficulty of breathing, Muscle ache, Chills, Sore throat, Runny nose, Headache, Chest pain, Pink eye (Conjunctivitis)

Causes:

- The virus that causes COVID-19 spreads easily among people, and more continues to be discovered over time about how it spreads. Data has shown that it spreads mainly from person to person among those in close contact (within about 6 feet, or 2 meters). The virus spreads by respiratory droplets released when someone with the virus coughs, sneezes, breathes, sings or talks. These droplets can be inhaled or land in the mouth, nose or eyes of a person nearby.
- In some situations, the COVID-19 virus can spread by a person being exposed to small droplets or aerosols that stay in the air for several minutes or hours called airborne transmission. It's not yet known how common it is for the virus to spread this way.
- It can also spread if a person touches a surface or object with the virus on it and then touches his or her mouth, nose or eyes, although this isn't considered to be a main way it spreads. Some reinfections of the virus that causes COVID-19 have happened, but these have been uncommon

1.2 CORONA VIRUS:

- Coronaviruses are a family of viruses that cause illness such as respiratory diseases or gastrointestinal diseases. Respiratory diseases can range from the common cold to more severe diseases

Ex:

Middle East Respiratory Syndrome (MERS-CoV)

Severe Acute Respiratory Syndrome (SARS-CoV)

- Coronavirus (nCoV) is a new strain that has not been identified in humans previously. Once scientists determine exactly what coronavirus it is, they give it a name (as in the case of COVID-19, the virus causing it is SARS-CoV-2).
- Coronaviruses got their name from the way that they look under a microscope. The virus consists of a core of genetic material surrounded by an envelope with protein spikes. This gives it the appearance of a crown. The word Corona means “crown” in Latin.

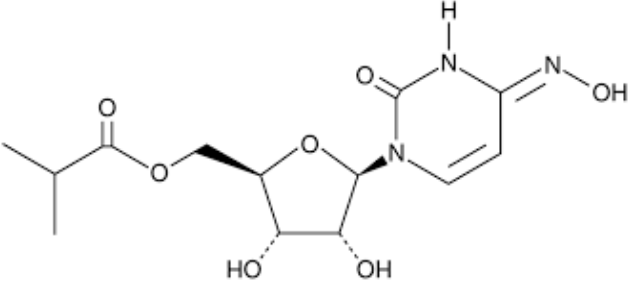
Coronaviruses are zoonotic, meaning that the viruses are transmitted between animals and humans. It has been determined that MERS-CoV was transmitted from dromedary camels to humans and SARS-CoV from civet cats to humans. The source of the SARS-CoV-2 (COVID-19) is yet to be determined, but investigations are ongoing to identify the zoonotic source to.

1.3 DRUGS USED IN CORONAVIRUS

- ❖ Hydroxychloroquine
- ❖ Favipiravir
- ❖ Remdesivir
- ❖ Molnupiravir
- ❖ Tocilizumab
- ❖ Itolizumab (only preliminary results available)
- ❖ Steroids: Dexamethasone, Methylprednisolone
- ❖ Low molecular weight Heparin
- ❖ Antibiotics - Azithromycin, Ivermectin
- ❖ Convalescent Plasma Therapy

2. DRUG PROFILE ⁶

INTRODUCTION	
Name	Molnupiravir
Official in	Not Official in any Pharmacopoeia
Description & Mechanism of action	<p>Molnupiravir is an orally bioavailable isopropylester cytidine analog being investigated to treat COVID-19. Molnupiravir is hydrolyzed in vivo to N4-hydroxycytidine, which is phosphorylated in tissue to the active 5'-triphosphate form, and incorporated into the genome of new virions, resulting in the accumulation of inactivating mutations, known as viral error catastrophe. A remdesivir resistant mutant mouse hepatitis virus has also been shown to have increased sensitivity to N4-hydroxycytidine. N4-Hydroxycytidine</p> <p>Molnupiravir is hydrolyzed to N4-hydroxycytidine, which distributes into tissues.² Once inside cells, N4-hydroxycytidine is phosphorylated to the 5'-triphosphate form.</p>

Structure										
Chemical Formula	C ₁₃ H ₁₉ N ₃ O ₇									
Mol. Weight	329.31 g/mol									
IUPAC Name	[(2R,3S,4R,5R)-3,4-dihydroxy-5-[(4Z)-4-(hydroxymino)-2-oxo-1,2,3,4-tetrahydropyrimidin-1-yl]oxolan-2-yl]methyl 2-methylpropanoate									
Categories	Antiviral drug									
Solubility	Soluble in water, Freely Soluble in methanol, Ethanol & DMSO.									
PROPERTIES										
State	White crystalline Solid									
CAS NO.	2349386-89-4									
Melting point	151-153°C									
Experimental properties	<table border="1"> <thead> <tr> <th>Property</th> <th>Value</th> </tr> </thead> <tbody> <tr> <td>Water solubility</td> <td>5.77 mg/mL</td> </tr> <tr> <td>Log P</td> <td>1.5</td> </tr> <tr> <td>pKa</td> <td>8.21</td> </tr> </tbody> </table>		Property	Value	Water solubility	5.77 mg/mL	Log P	1.5	pKa	8.21
Property	Value									
Water solubility	5.77 mg/mL									
Log P	1.5									
pKa	8.21									

2.1 INTRODUCTION TO DOSAGE FORM:

Sr. No.	Brand Name	Manufacturer	Dosage form	Dose
1	LAGEVRIO 200mg , 400mg	Merck Sharp & Dohme Corp.	Capsule	Molnupiravir 200 mg Molnupiravir 400 mg

3 Experimental Work

3.1 METHOD DEVELOPMENT FOR ESTIMATION OF MOLNUPIRAVIR BY RP-HPLC.

3.1.1 Selection of wavelength

Standard solution of Molnupiravir (10 µg/mL) in Methanol was scanned between 200-400 nm using UV-visible spectrophotometer. Wavelength was selected from the spectra of above solution. Molnupiravir show response at 235 nm and 271 nm, but it shows good response at 235 nm hence 235 nm was selected for further work.

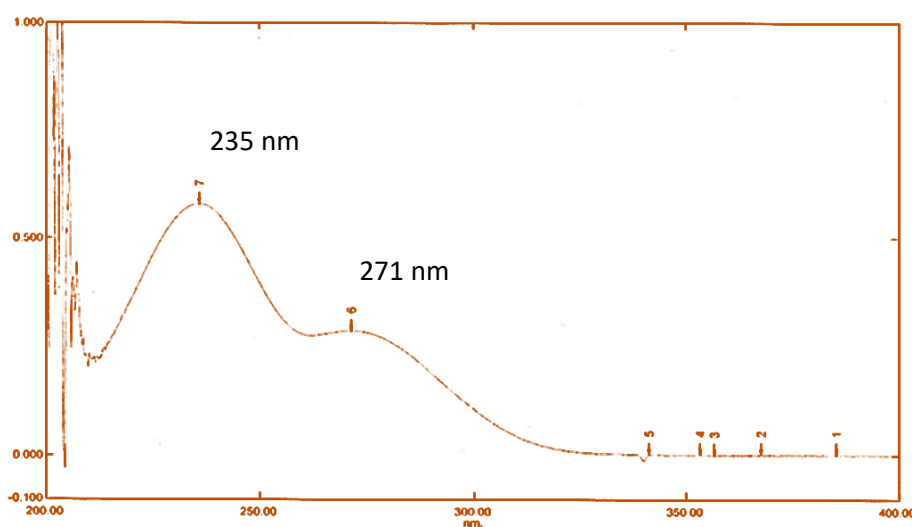


Figure 3.1: UV Spectrum of Molnupiravir (10µg/ml) showing selection of wavelength detection.

3.1.2 Preparation of standard solutions:

A. Molnupiravir standard stock solution: (1000 µg/ml)

Accurately weighed quantity of 50 mg of Molnupiravir standard was transferred to a 50 mL volumetric flask. Added about 25 ml of diluent and sonicated to dissolve. Final volume was made up to the mark with diluent and mixed.

B. Preparation of standard solution of Molnupiravir (100 µg/mL):

Taken 5 mL from the Molnupiravir stock solution and transferred to 50 mL volumetric flask and volume made up to the mark with diluent and mixed. This solution was used in particular trials.

C. Preparation of standard solution of Molnupiravir (10 µg/mL):

Taken 5 mL from the Molnupiravir stock solution and transferred to 50 mL volumetric flask and volume made up to the mark with diluent and mixed. This solution was used in selection of wavelength.

3.1.3 Preparation of synthetic Mixture and placebo mixture

A. Preparation of synthetic mixture

Mixed Molnupiravir, MCC, Polyvinylpyrrolidone K-30, Crossprovidone, Sodium stearyl fumarate, in proportions of 200:50:10:10:5 respectively in laboratory.

B. Preparation of Placebo

Mixed MCC, Polyvinylpyrrolidone K-30, Crossprovidone, Sodium stearyl fumarate, in proportions of 50:10:10:5 respectively in laboratory.

3.1.4 Selection of Mobile Phase:

Trail contains various mobile phase which are considered of Methanol, Water, Acetonitrile and Buffer solution in different proportions and different volumes at different flow rate were tried.

On the basis of various trails the ratio of Buffer solution (0.1% Orthophosphoric acid) and Acetonitrile (85:15 % V/V) at 1.0 mL/min flow rate, proved to be better than the other mixture in terms of peak shape, theoretical plate and asymmetry.

A. Preparation of Buffer solution(0.1% Orthophosphoric acid):

Diluted 1.0 ml of Orthophosphoric acid into 1000 ml of Milli-Q water and Mixed.

B. Preparation of Mobile Phase

Prepared a degased Mixture of buffer solution (0.1% Orthophosphoric acid) and acetonitrile in ratio of 85:15 % V/V and sonicated for 10 min.

C. Preparation of Diluent

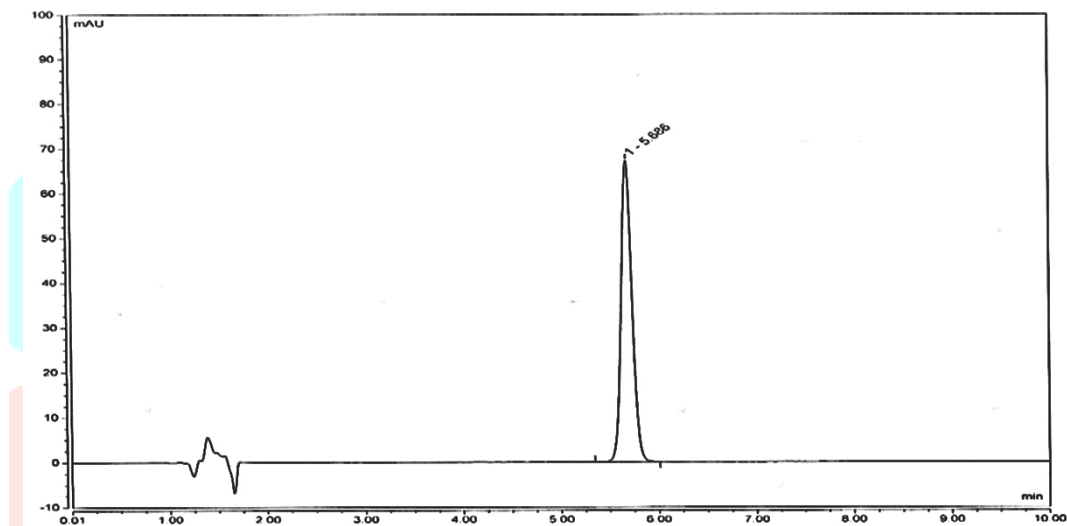
Prepared a degased Mixture of Water and Methanol in ratio of 50:50 % V/V and sonicated for 10 min.

D. Preparation of standard solutions (100 µg/mL)

Accurately weighed quantity of 50 mg of Molnupiravir standard was transferred to a 50 mL volumetric flask. Added about 25 ml of diluent and sonicated to dissolve. Volume was made up to the mark with diluent and mixed. Further diluted 5.0 ml of this solution to 50 ml with diluent and mixed.

E. Preparation of sample solutions (100 µg/mL)

Calculate average net content using 20 capsules. Accurately weighed amount of sample powder equivalent to 200 mg of Molnupiravir was transferred in to 200 ml volumetric flask. Added about 140 ml of diluent was added and solution was sonicated for 30 min to ensure complete solubilisation of drug. Then volume was made up to mark with diluent and mixed. Further diluted 5.0 ml of this solution to 50 ml with diluent and mixed. Filtered solution through 0.45 µm membrane filter paper.

Chromatographic conditions:**Column:** Kromasil 100-5-C18 (150 mm x 4.6 mm) 5 μ **Mobile Phase:** Buffer solution (0.1% Orthophosphoric acid): Acetonitrile
(85:15 % v/v)**Flow Rate:** 1.0 ml/min**Detection Wavelength:** 235 nm**Injection volume:** 10.0 μ l**Run time:** 10 min

3.1 Chromatogram of Molnupiravir in buffer (0.1% OPA): Acetonitrile (85:15%v/v) (Flow rate-1.0 ml/min).

- **Observed values for system suitability test:**

1. **Column efficiency (N):** Number of theoretical plates observed for Molnupiravir was 8803
2. **Symmetry factor (S):** Tailing factor observed for Molnupiravir was 1.18

Table 3.1 Results for system suitability test.

Parameters	Data observed
Theoretical plates per column	8803
Symmetry factor/Tailing factor	1.18

System suitability / System precision

- Procedure

System suitability and precision were demonstrated by injecting five replicate injections of standard solution prepared as per the test method. The peak area of analyte of replicate standard injection was recorded. The theoretical plate and tailing factor for analyte peak were evaluated from standard solution. The precision was evaluated by computing the relative standard deviation for the peak area of these replicate injections.

- Acceptance criteria

The column efficiency for analyte peak should not be less than 2000 theoretical plates.

The tailing factor should not be more than 2.0

The relative standard deviation for five replicates standard injections should not be more than 2.0%.

3.1.2.1 Filter compatibility and saturation

- Procedure

The filter saturation was verified by preparing the assay samples with optimized samples preparation and analyzed the samples by discarding different volume of sample solution. The assay of these samples was determined.

- Acceptance criteria

The difference between the unfiltered and filtered samples should NMT 2.0 %

Table 3.2 Filter Compatibility and Saturation

Discarded volume	% of Molnupiravir	% Difference
Unfiltered	100.3	-NA-
After 3 ml	99.5	-0.8
After 5 ml	100.2	-0.1
After 7 ml	100.1	-0.2

❖ Conclusion:

After performing filter saturation study using 0.45 µm Membrane filter which indicates that this filter is compatible for analysis of sample. We recommended using 0.45 µm membrane filters with discard volume 5 ml for analysis.

3.1.2.2 Linearity & Range

- Procedure

The linearity of detector response for Molnupiravir was demonstrated by preparing solutions of Molnupiravir working standard over the range of 50-150 % of standard concentrations. These solutions were injected into the HPLC system and the area of analyte peak was recorded. A graph of concentration vs. analyte peak response was plotted. The concentration co efficient between concentration & analyte peak response and Y- intercept of the correlation plot was evaluated.

Preparation of Linearity stock solution (1000 ppm)

Accurately weighed quantity of 50 mg of Molnupiravir standard was transferred to a 50 mL volumetric flask. Added about 25 ml of diluent and sonicated to dissolve. Volume was made up to the mark with diluent and mixed.

50% solution preparation (50 µg/mL): 2.5 mL from stock solution was taken and transferred into 50 mL flask and made up the volume with diluent.

80% solution preparation (80 µg/mL): 4.0 mL from stock solution was taken and transferred into 50 mL flask and made up the volume with diluent.

100% solution preparation (100 µg/mL): 5.0 mL from stock solution was taken and transferred into 50 mL flask and made up the volume with diluent.

120% solution preparation (120 µg/mL): 6.0 mL from stock solution was taken and transferred into 50 mL flask and made up the volume with diluent.

150% solution preparation (150 µg/mL): 7.5 mL from stock solution was taken and transferred into 50 mL flask and made up the volume with diluent.

- Acceptance criteria

The correlation coefficient should not be less than 0.990.

Y- Intercept was ± 2 % of 100 % linearity level response

Table 3.3 Linearity parameter

Linearity Level (%)	Conc. of Molnupiravir (µg/ml)	Peak area of Molnupiravir
50	50	1112
80	80	1715
100	100	2218
120	120	2625
150	150	3320

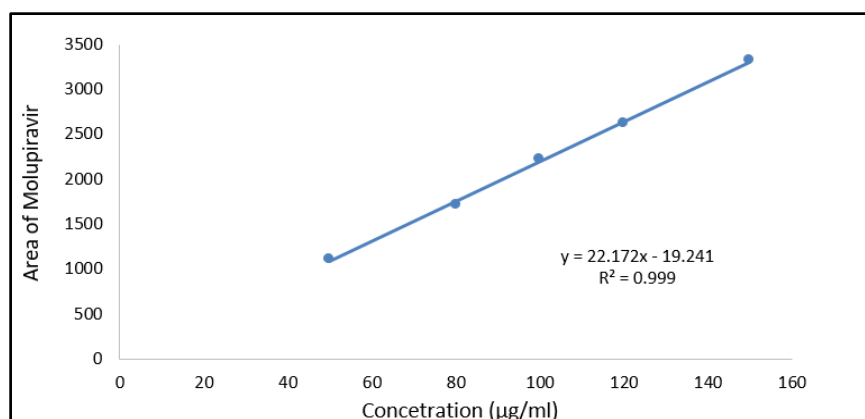


Figure 3.2: Linearity curve of Molnupiravir

3.1.2.3 Method precision

- Procedure

Method precision was demonstrated by preparing six samples as per the test method representing a single batch. The assay of these samples was determined and the precision and the precision of method was evaluated by computing the percentage relative standard deviation of assay results.

- Acceptance criteria

% RSD for assay of six replicate preparations should not more than 2.0.

Table 3.4 Method precision result

Sample Set	% Assay (Molnupiravir)
1	99.6
2	100.6
3	100.0
4	99.0
5	99.5
6	99.2
Average	99.7
% RSD	0.58

- ❖ Conclusion:

The low % RSD observed on the assay values indicates that method is precise.

3.1.2.4 Accuracy

- Procedure

The accuracy of the test method was demonstrated by preparing recovery samples i.e. spiking of with known quantities of API in placebo at the level of 50%, 100%, and 150% of target concentration. The recovery samples were prepared in triplicate. The above samples were injected and the percentage recovery for amount added was estimated. The precision of the recovery was determined by computing the relative standard deviation of triplicate recovery results.

Preparation of recovery solutions:

50% Recovery: Weighed accurately 50 mg API and 42.5 mg of placebo in 100 ml of volumetric flask.

100% Recovery: Weighed accurately 100 mg API and 42.5 mg of placebo in 100 ml of volumetric flask.

150% Recovery: Weighed accurately 150 mg API and 42.5 mg of placebo in 100 ml of volumetric flask.

Note: Further procedure for 50%, 100%, and 150% followed as per Sample preparation.

- Acceptance criteria

The recovery should be 98.0- 102.0 % and the RSD should NMT 2.0 %

3.1.2.5 Accuracy

Table 3.5 Result of Accuracy

Level	Sample Set	Weight Of Placebo (mg)	API Added (mg)	API Recovered (mg)	% Recovery	% Mean	% RSD
50%	Set 01	42.5	50	49.7	99.4	99.8	0.53
	Set 02	42.5	50	49.8	99.6		
	Set 03	42.5	50	50.2	100.4		
100%	Set 01	42.5	100	101.2	101.2	100.4	0.72
	Set 02	42.5	100	99.8	99.8		
	Set 03	42.5	100	100.2	100.2		
150%	Set 01	42.5	150	148.1	98.7	98.9	0.82
	Set 02	42.5	150	146.3	98.2		
	Set 03	42.5	150	149.9	99.8		

❖ **Conclusion:**

The result of this study was found to be within the acceptance criteria of method validation (i.e. the recovery is 98.0 – 102.0 % and the RSD is NMT 2.0 %), this proves that the test method is accurate for the estimation of Molnupiravir in Molnupiravir Capsule.

3.1.2.6 Specificity

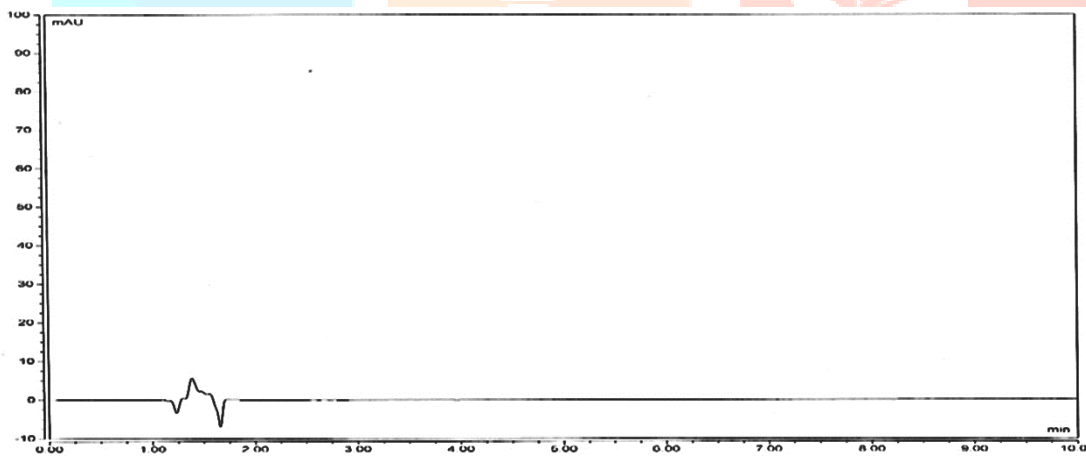


Figure 3.3: Chromatogram of Diluent

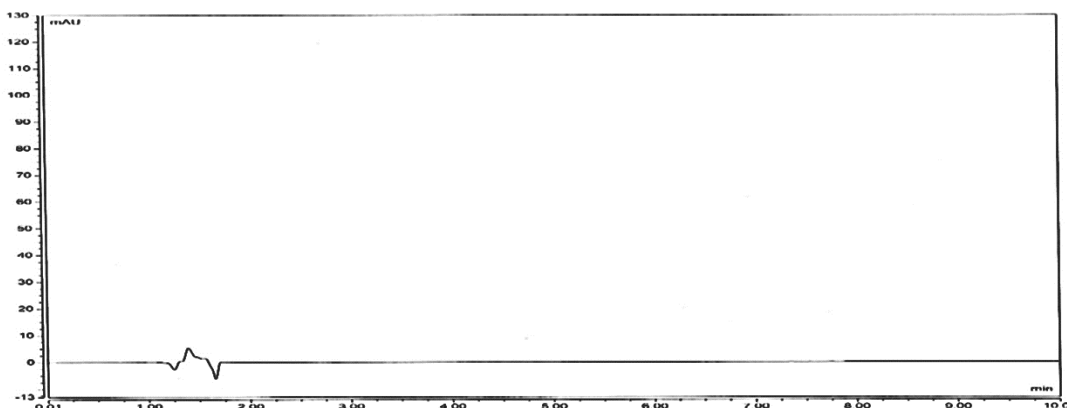


Figure 3.4: Chromatogram of Placebo

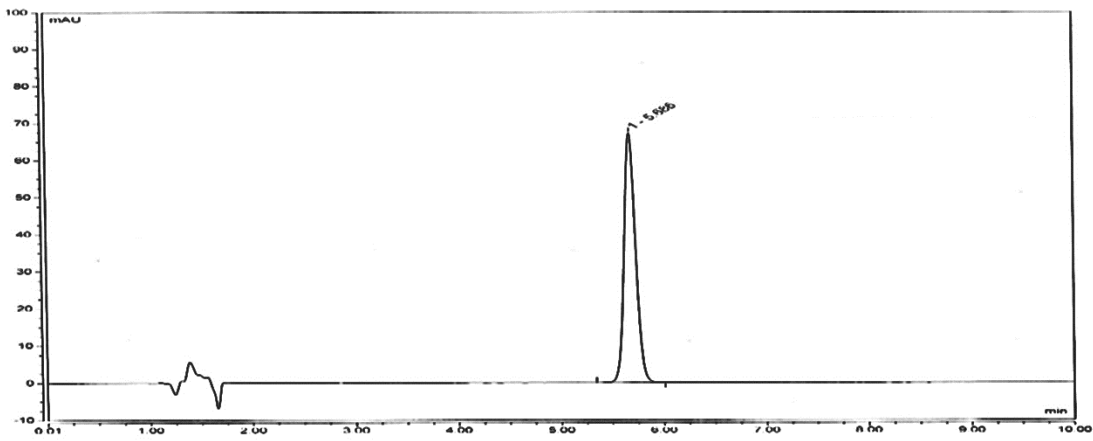


Figure 3.5: Chromatogram of Molnupiravir Standard

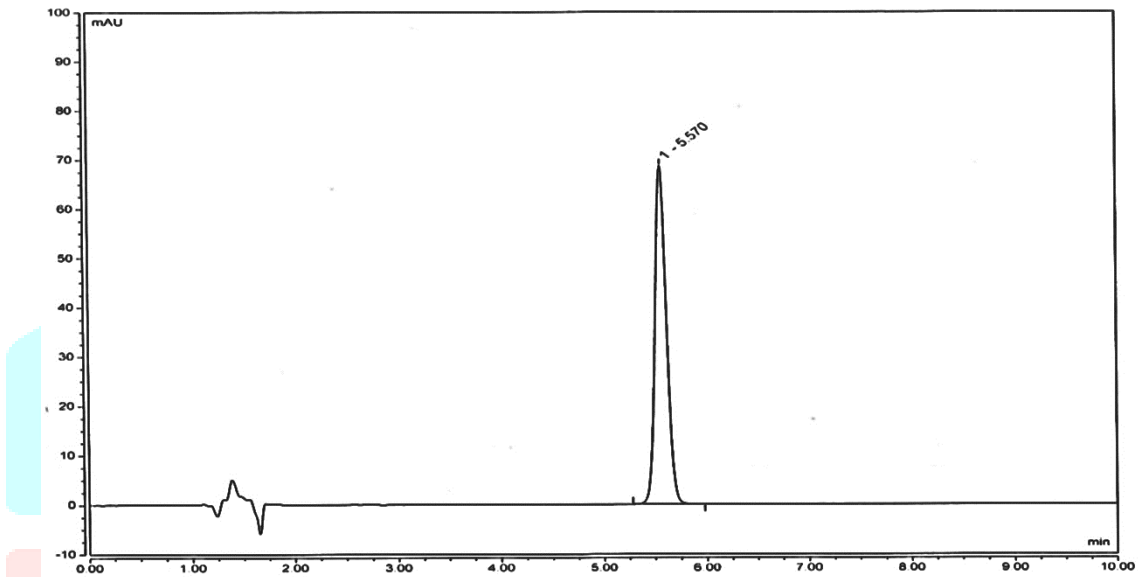


Figure 3.6: Chromatogram of Molnupiravir sample

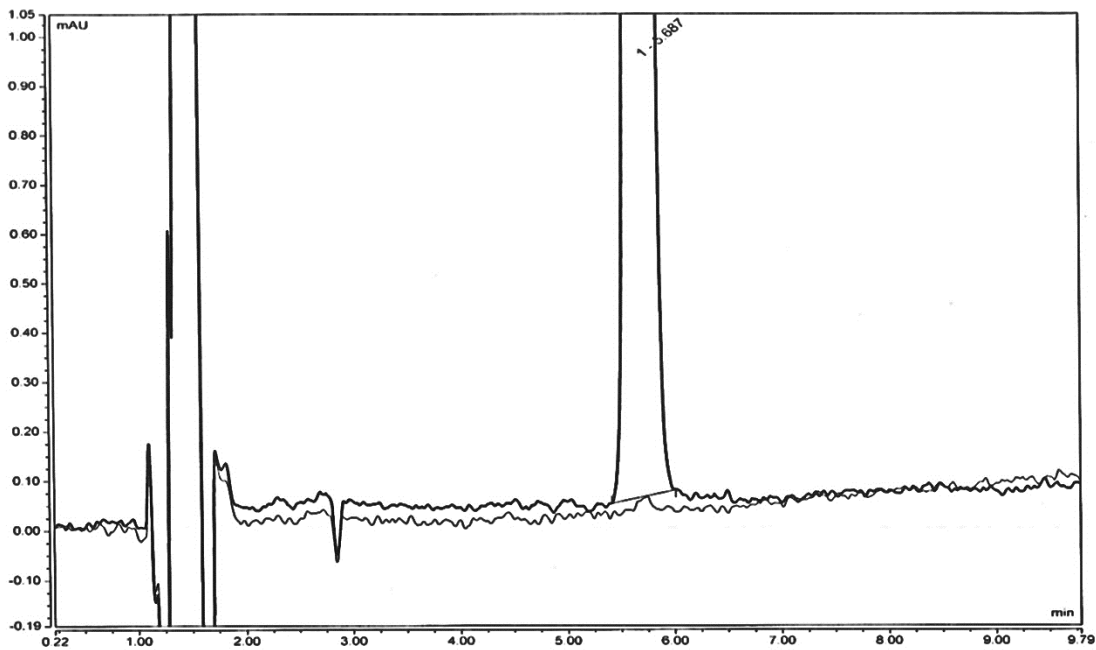


Figure 3.7: Overlay Chromatogram of Molnupiravir Placebo and Sample

❖ Conclusion:

The result of the study indicate that there was no interference from blank and placebo with analyte and method is specific for the estimation of assay of Molnupiravir in Molnupiravir Capsule.

3.1.2.7 Robustness

According to robustness there is minor but deliberate change made in chromatographic Parameters.

• Procedure

Preparation of standard solution (100 ppm)

Accurately weighed quantity of 50 mg of Molnupiravir standard was transferred to a 50 mL volumetric flask. Added about 25 ml of diluent and sonicated to dissolve. Volume was made up to the mark with diluent and mixed. Further diluted 5.0 ml of this solution to 50 ml with diluent and mixed.

Change in organic phase ratio of mobile phase: Buffer: ACN (83:17) %v/v and Buffer: ACN (87:13) %v/v

Change in flow rate: 0.9 ml/min and 1.1 ml/min

• Acceptance criteria

The column efficiency for analyte peak should not be less than 2000 theoretical plates.

The tailing factor should not be more than 2.0

The relative standard deviation for five replicates standard injections should not be more than 2.0%.

3.1.2.8 Robustness

Table 3.6 Robustness parameter

Condition	Theoretical plate	Tailing factor	Retention Time (min)	% RSD
Normal	8103	1.17	5.57	0.27
Organic mobile phase ratio: [Buffer : ACN (87:13) %v/v]	7992	1.19	6.81	0.23
Organic mobile phase ratio: [Buffer : ACN (83:17) %v/v]	8315	1.16	4.72	0.18
Flow rate: 0.9 ml/min	8079	1.17	6.20	0.32
Flow rate: 1.1 ml/min	8243	1.15	5.01	0.19

❖ Conclusion:

Theoretical Plates and Asymmetry value are from the first injection of the system suitability set were found within the acceptance criteria as per system suitability. So, the study proves the reliability of test method for minor changes in chromatographic condition. Hence method can be termed as robust.

3.1.2.9 Ruggedness (Intermediate Precision)

To measure of reproducibility test results under the variation in conditions normally expected different laboratory, different analyst, different instrument and different day.

• Procedure

Ruggedness of method was verified by preparing the standard solution and six replicate of assay samples as per test procedure on different day and analyzed on HPLC.

• Acceptance criteria

The column efficiency for analyte peak should not be less than 2000 theoretical plates.

The tailing factor should not be more than 2.0

The relative standard deviation for five replicates standard injections should not be more than 2.0%.
% RSD for assay of six replicate preparations should not more than 2.0.

The difference between method precision and Intermediate Precision samples should NMT 3.0 %

3.1.2.10 Ruggedness (Intermediate Precision)

Table 3.7 Ruggedness (Intermediate Precision) result

Sample Set	% Assay (Molnupiravir)
1	98.3
2	99.2
3	99.3
4	100.1
5	97.9
6	98.6
Average	98.9
% RSD	0.80

❖ Conclusion:

Theoretical Plates and Asymmetry value were found within the acceptance criteria. The low % RSD observed on the assay values indicates that method is precise. Difference between method precision and Ruggedness (Intermediate Precision) was found 0.8%. Hence the study proves the method is rugged for analysis of Molnupiravir in Molnupiravir capsule.

3.2.1.11 Stability of analytical solution

- Procedure

Stability of standard solution and sample solution were established at room temperature (about 25°C) for minimum 24 hours. Standard solution and sample solution were prepared as per test method.

- **Acceptance criteria:**

The response of standard and sample solution should not differ by more than 2.0% from initial response for the accepted storage time.

Table 3.8 Stability of analytical solution for standard solution

Time (hrs.)	Peak area	% deviation from initial area
Initial	2199	-
7 HR	2193	0.3
23 HR	2180	0.9
29 HR	2173	1.2

Table 3.9 Stability of analytical solution for sample solution

Time (hrs.)	Peak area	% deviation from initial area
Initial	2190	-
7 HR	2195	-0.2
23 HR	2168	1.0
29 HR	2157	1.5

❖ **Conclusion:**

The Standard and Sample solution of Molnupiravir is stable at room temperature (i.e. about 25°C) up to 29 hours

3.10 Method Validation Summary

Parameter		Molnupiravir
Concentration range ($\mu\text{g/ml}$)		50 - 150 ppm (50-150%)
Regression equation $y = mx + c$		$y = 22.172x - 19.241$
Correlation coefficient		0.999
System Suitability		% RSD : 0.11 % Theoretical plates : 8003 Tailing factor : 1.16
Method Precision		99.7 % (% RSD: 0.58%)
Accuracy (%Recovery)	50%	99.8 % (% RSD: 0.53 %)
	100%	100.4 % (% RSD: 0.72 %)
	150%	98.9 % (% RSD: 0.82 %)
Specificity		No interference from blank and placebo with analyte so method is specific.
Robustness		Theoretical Plates and Asymmetry value are found within the acceptance criteria. % RSD found to be less than 2.0 %.
Ruggedness (Intermediate Precision)		98.9 % (RSD: 0.80%) Difference between method precision and Intermediate Precision : 0.8%
Stability of analytical solution		The Standard and Sample solution is stable at room temperature (i.e. about 25 ⁰ C) up to 29 hours.

ASSAY OF MOLNUPIRAVIR IN PHARMACEUTICAL DOSAGE FORM BY DEVELOPED RP-HPLC METHOD:

Table 3.11 Assay of Molnupiravir by developed RP-HPLC method

Brand Name	Label Claim (mg)	Amount found (mg)	% Assay
MOLFLU (Dr Reddy'S Laboratories LTD)	200	200.4	100.2
		201.6	100.8
	Mean	201.0	100.5
MOLUSAFE (Astraea Life sciences PVT LTD)	200	197.6	98.8
		199.4	99.7
	Mean	198.5	99.3

SUMMARY & CONCLUSION

8.1 Summary

There is no analytical work has been available regarding HPLC method for Molnupiravir in a literature. A novel attempt in a field of research has been made to develop and validate assay method and to demonstrate degradation profile via RP-HPLC.

A simple and rapid RP-HPLC method has been developed for determination of Molnupiravir in pharmaceutical dosage form. Separation has been achieved using Kromasil 100-5-C18 (150 mm x 4.6 mm) 5 μ column using Buffer solution (0.1% OPA): Acetonitrile (85:15, v/v). Detection wavelength is 235 nm and retention time of Molnupiravir is about 5.50 min with 1.0 ml/min flow rate..

The RP HPLC method for estimation of Molnupiravir was validated as per ICH Guideline Q2 (R1). Method Validation Parameters like System Suitability, System Precision, Filter Compatibility, Method Precision, Linearity, Accuracy, Specificity, Robustness, Ruggedness, and Stability of analytical solutions were performed. All parameter results are found within the acceptance limit.

8.2 Conclusion

RP-HPLC method has been developed and validated for the estimation of Molnupiravir from Molnupiravir Capsule dosage form. The method was found to be specific. The present method has been found to be adequately robust and cost effective. The method was validated as per ICH guidelines. All parameter and results are found within the acceptance limit.

So, we can conclude that Developed Stability indicating RP-HPLC method is found to be linear, specific, accurate, robust, rapid and cost effective. Thus, the proposed method can be used in routine quality control analysis for estimation of Molnupiravir from Molnupiravir Capsule dosage form.

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