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Research Article

Stability Indicating RP-HPLC Method Development for the Estimation of Molnupiravir in Capsule Dosage Form

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ABSTRACT

In recent years much more attention has gained by antiviral drugs because of severe acute respiratory syndrome coronavirus-2 (SARS-CoV) infection. Molnupiravir is one of the favorable drugs for SARS-CoV-2 treatment. The present study aimed to develop and validate a simple, rapid, stable, selective, sensitive, accurate, robust, and economical RP-HPLC method for determining molnupiravir in its capsule dosage form. The chromatographic separation was achieved on inert sustain C18 column (250 mm x 4.6 mm x 5 µ) at 40°. Isocratic elution was performed with 25 mM KH_2PO_4 buffer (pH 3.0) and methanol (60:40 v/v) as mobile phase at flow rate of 1.0 mL/min with 50 µL injection volume. The detection was conceded out at 242 nm. The developed RP-HPLC method yielded a suitable retention time of 4.2 minutes for molnupiravir. The developed method was validated according to the International Council on Harmonization (ICH) guidelines and established to be linear in the range of 10 to 70 µg/mL with a linear regression coefficient of 0.9993. The %RSD for the method precision and system precision was found to be less than 2.0%. The %assay of the formulation is 101.52%. The LoD and LoQ were found to be 0.25 and 0.75 µg/mL, respectively. The specificity of the method established using forced degradation studies in which the drug is subjected to the stressed conditions such as thermal, acidic, basic oxidative and photolytic degradation. The developed and validated RP-HPLC method for molnupiravir takes short time and can be used for routine quality analysis of marketed Molnupiravir in capsule dosage form.

Introduction

WHO declared the outbreak of coronavirus disease caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in January of 2020 a public health emergency of international concern, and it was declared a pandemic by March 2020.[1-3] Early development and discovery of molnupiravir began in 2013 with a focus on finding an orally available, direct acting antiviral agent for the treatment of infection by encephalitic new world alphavirus (VEEV) Venezuelan equine encephalitis virus.[4] Remidesivir was the first FDA-approved drug for treating patients with COVID-19[5-6], however, its effectiveness is doubtful[7] put emphasis on the need to develop new antiviral drugs. Molnupiravir is another promising drug for the treatment of patients with COVID-19 which targets the RNA-dependent RNA polymerase (RdRp) of the SARS-CoV-2.

Molnupiravir is an isopropyl ester prodrug of the nucleoside analog β-d-N^4-hydroxycytidine (NHC or EIDD-1931) as shown in Fig. 1.[8] It inhibits SARS-COV-2 replication in human lung tissue, in ferret blocks SARS-CoV-2 transmission and reduces SARS-CoV-2 RNA in patients.[9] Antiviral drugs repeatedly target viral polymerases and function as nucleoside analogs that terminate RNA chain elongation. Such chain terminating antivirals are generally ineffective against SARS-

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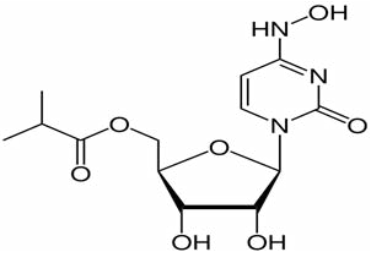

Fig. 1: Structure of Molnupiravir

CoV-2 because coronaviruses carry an exonucleolytic proofreading activity that can remove misincorporated nucleotides from the nascent RNA 3'end.[10,11]

Exposure to NHC was generally dose-proportional in all species following oral administration of molnupiravir. It is rapidly converted to NHC and unstable in plasma. Once NHC is absorbed into animal plasma it is broadly distributed in tissues where rapid conversion to the active NHC-2'-triphosphate (EIDD-2061) happens. If ongoing clinical trials results as expected, molnupiravir is considered to become an important tool to counter the effects of the COVID-19 pandemic.[12,13]

HPLC is an analytical tool which is able to detect, separate and quantify the drug, its various impurities and drug-related degradants that can form on synthesis or storage.[14] Molnupiravir is not found in Pharmacopeia. A literature search for the analytical methods for molnupiravir shows limited results, in that there is an LC-MS/MS method for the determination of molnupiravir and its metabolite in human plasma and saliva[15] and stability indicating RP-HPLC method for determination of molnupiravir applied using nanoformulations in permeability studies.[16] According to the guidelines of the International Council on Harmonization (ICH) for the determination of drugs after stability analysis requires the development of stability indicating assay methods (SIAMs) appropriately. The stability of molnupiravir was evaluated with forced degradation studies. In this study, we present a simple, rapid, robust, stable, precise and accurate RP-HPLC method for the determination of molnupiravir in capsule dosage form. This method was developed and validated according to the ICH guidelines.

Materials and Methods

Chemicals and Reagents

Molnupiravir working standard was procured from Central Drug Testing Laboratory, Mumbai with claimed potency [99.83% as is basis]. MOLONOVA (400 mg) Capsules (Molnupiravir) was procured from the local market. HPLC grade methanol from Rankem, potassium dihydrogen phosphate from Avra Synthesis LTD, orthophosphoric acid from SRL chem, 0.45 µm high flow nylon membrane filter purchased from Axiva Sichem Pvt. Ltd and water- milli-Q Grade were used.

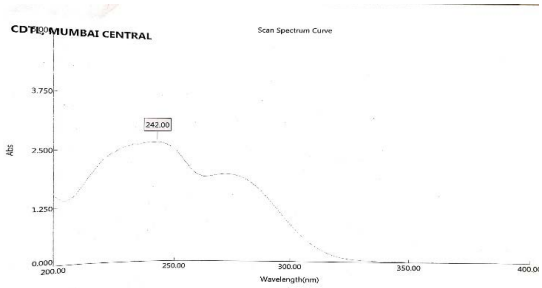

Fig. 2: Molnupiravir UV spectrum

Instrumentation

Lab India UV-vis spectrometer equipped with UV Win Lab software was used for all the spectrophotometric measurements. Thermo scientific Dionex ultimate 3000 using Chrome Leon 7.2.6 software with LC instrument control was used for chromatography. All weighing's were done with the Sartorius Analytical Balance. Digital pH meter was used for all pH adjustments. HPLC equipped with a Waters 2996 (PDA) photodiode array detector was used for degradation studies. The column used was inert sustain 25 cm × 4.6 mm & 5 µ particle size

Selection of Solvent (Diluent)

Based on the solubility and chemical nature of molnupiravir, the HPLC grade water and methanol (50:50) were selected as a diluent for preparing standard and sample solutions.

Selection of Wavelength

A Total of 10.0 mg of molnupiravir was transferred to the 100 mL volumetric flask and the volume was made up to the mark with diluent (100 µg/mL) and from that stock solution further dilutions were made to make the concentration of 10 µg/mL. The solution was scanned in the 200 to 400 nm range of the maximum absorbance observed at 242 nm (Fig. 2).

Preparation of Standard Solution

Transferred approximately 20 mg of molnupiravir standard in 20 mL of volumetric flask, dissolved it by sonication with sufficient amount of diluent, and made up the volume up to Merck (1000 µg/mL). Then further dilutions were made to make the 40 µg/mL concentration.

Analysis of Marketed Formulation

Transferred the components 1 capsule equivalent (400 mg) to 100 mL flask and volume was made with 100 mL diluent (4000 µg/mL) and filtered through 0.45 µ nylon filter. Further dilutions were made to make the concentration of 40 µg/mL.

Preparation of Mobile Phase

Potassium dihydrogen phosphate (KH_2PO_4) 25 mM was prepared, pH adjusted with orthophosphoric acid to 3.0 and methanol in the ratio of 60:40 v/v was used as a mobile phase. The mobile phase was vacuum filtered through

0.45 µm nylon membrane filter and sonicated using ultra sonicator.

Analytical Method Validation

The developed RP-HPLC method was validated as per ICH Q2 (R1) guidelines[17] with respect to various parameters such as precision, linearity, sensitivity, accuracy, and robustness.

Linearity

From the standard solution of molnupiravir, aliquots were prepared in the concentration range of 10 to 70 µg/mL. By constructing the graph by plotting concentration verses area obtained from the response. The linear calibration plot was constructed by analyzing the concentrations over the selected range. The response for the drug was linear in the concentration range between 10–70 µg/mL. The results were shown in Table 1.

Precision

Precision expresses the degree of reproducibility of responses of repeated measurements. The more responses give better precision & the smaller the error will be.

- *System precision*

Six replicate injections of a standard solution of molnupiravir (40 µg/mL) were injected into the HPLC system. The mean, SD and %RSD were calculated and reported. Results were shown in Table 2.

- *Method precision*

Sample solutions of 40 µg/mL were prepared and 6 injections were injected into the HPLC system with the developed method then mean, SD and %RSD values were calculated and the results were shown in Table 3.

- *Intraday precision*

Freshly prepared standard and sample solutions were injected on different time interval on same day to check the repeatability of the developed method. The results were shown in Table 3.

- *Intermediate precision*

Freshly prepared standard and sample solutions were injected on two different days to check their reproducibility on two different days. The mean, SD and %RSD is calculated as shown in Table 3.

Accuracy or Recovery (Standard addition method)

Accuracy refers to the closeness of the measured value of a quantity corresponds to its "true" value. In that accepted either true value or an accepted reference value and the estimated value.

Accuracy studies was carried out by standard addition method where known concentration of molnupiravir (110, 120 and 130%) of standard solution was added to pre-analysed formulation and check the individual recovery and mean recovery values by calculating the amount found and amount added for molnupiravir as shown in Table 4. The good recovery of the spiked drug was obtained at each added concentration, which shows that the method was accurate.

Robustness

The terms robustness and ruggedness demote to the ability of an analytical method to remain unaffected by small variations in the method parameters (mobile phase content, column temperature, etc.) and influential environmental factors (room temperature, air humidity, etc.) and characterize its reliability during normal usage. Deliberate changes were made in temperature, flow, wavelength, and mobile phase in the estimation of molnupiravir solution which shows no significant deviations in the results with, indicating the reliability and results were shown in Table 5.

LoD and LoQ

Limit of detection (LoD) & Limit of Quantification (LoQ) were calculated based on the standard deviation of the y-intercept and slope of the calibration curve. LoD = 3.3 δ/S, LoQ = 10 δ/S. Where δ denotes the standard deviation of the regression line and s denotes the slope obtained from the calibration curve. The sensitivity of the current method was estimated in terms of LoD and LoQ.

Specificity

The specificity of the method was established by demonstrating no interference from degradation products. This was demonstrated by carrying out forced degradation of the sample by exposing solid & liquid state degradation. The samples were prepared and injected into HPLC equipped with a Waters 2996 PDA (Photodiode array) detector as per developed chromatographic and instrumental conditions. Forced degradation of the molnupiravir was carried out under acidic, basic, thermal, oxidative, hydrolytic and photolytic conditions.

Acidic Degradation

Molnupiravir (100 µg/mL) was refluxed and evaporated for 1-hour on water bath at 70°C with 10 mL hydrochloric acid (0.1N) and the same concentration was left in HCL at room temperature to cool. After this period, each solution was neutralized, filtered, and had the volume reconstituted with diluent to produce concentration equivalent to 40 µg/mL.

Basic Degradation

Molnupiravir (100 µg/mL) was refluxed & evaporated for 5 minutes on a water bath at 70°C with 10 mL Sodium hydroxide (0.01N) and the same concentration was left in NaOH for cooling at room temperature. After this period, each solution was neutralized, filtered, and had the volume reconstituted with diluent to produce a concentration equivalent to (40 µg/mL).

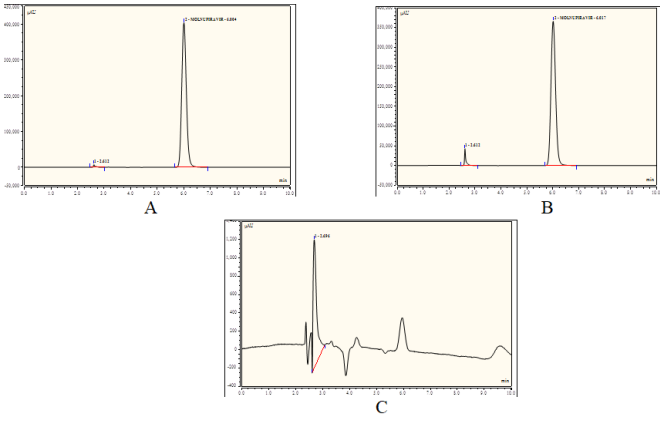

Fig. 4: A] Chromatogram of Molnupiravir standard solution (40 µg/mL) B] Chromatogram of Molnupiravir sample solution (40 µg/mL) C] chromatogram of blank solution

Oxidative Degradation

In 100 µg/mL of molnupiravir was refluxed & evaporated at 70°C with 10 mL of 3% hydrogen peroxide for 30 minutes on water bath. After that filtered and completed to volume with diluent (40 µg/mL).

Thermal Degradation

For 10 mg of molnupiravir in solid state was spread to 1-mm thickness in petri dish and kept in the oven at 70°C for 1-hour. This sample was taken into 100 mL volumetric flask, dissolved and diluted with diluent (100 µg/mL). Further dilution was made to make 40 µg/mL.

Photolytic Degradation

For 10 mL of 100 ppm solution of molnupiravir is kept under the UV light for 24 hours. After that the solution was completed to volume with diluent (40 µg/mL).

Hydrolytic Degradation

For 10 mL of 100 ppm solution of molnupiravir is evaporated on water bath at 70°C for 1 hour. After cooling that solution was completed to volume with diluent (40 µg/mL).

All these degraded products were injected into the HPLC system equipped with the PDA detector following the developed method and the results were shown in Table 7. All the degraded peaks in the chromatogram were shown in Fig. 3. The main peak of the drug for peak purity by calculating the percentage of degraded amount and percentage of the active amount with forced degradation is carried out to produce representative samples for developing stability indicating methods for drug substances and drug products.[18]

Results

The typical chromatogram of standard, sample and blank solution with the optimized method as shown in Fig. 4, and Table 3.

Table 1: Optimized chromatographic conditions

Program	*Isocratic*
HPLC system	Thermo ultimate 3000
Column	Inert sustain 25cm × 4.6 mm & 5 µ
Mobile phase	25 mM KH_2PO_4 buffer (pH 3.0): Methanol (60:40v/v)
Diluent	Water: ethanol (50:50)
Standard solution concentration	Molnupiravir stock solution (100 ppm)
Flow rate	1.0 mL/minutes
Run time	10 minutes
Wavelength	242 nm
Injection volume	50 µL
Column oven temperature	40°C
Retention time	6.0 minutes
Detector	UV-vis

Table 2: Molnupiravir linearity study in the range of 10–70 µg/mL

Linearity Level	*Concentration*	*Area*
1	10	20756.61
2	20	42909.61
3	30	60812.44
4	40	83830.22
5	50	101463.3
6	60	123042.1
7	70	141593.0

Method validation

Linearity

Linearity tests were performed in which different concentration sample vs. area were performed and results were obtained as y = 2012.2x + 1568.9 R^2=0.9993 which is within specifications as in Fig. 5.

Precision

Then precision tests were performed in which interday, intraday, system precision, and method precision is performed in which any of the test %RSD was not more than 2.00%.

Accuracy or Recovery

Accuracy test results at various levels of concentration are shown in Table 4, in which %mean recovery is 100.29% which is within limit for 110, 120, and 130%. Hence the method is accurate. The %RSD results for this study was found to be <2.0% with a corresponding percentage recovery value.[19]

Robustness

By deliberately changing the parameters, which are wavelength, flow & temperature robustness test is

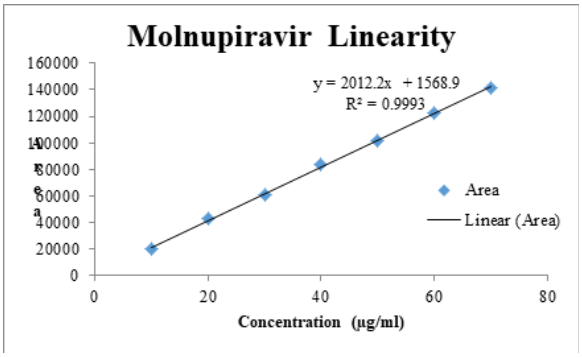

Fig. 4: Linearity curve of molnupiravir in the range of 10–70 µg/mL

performed in which the reliability of the method was detected and %RSD is NMT 2.00% (Table 5).

LoD and LoQ

The LoD and LoQ found with the linearity curve are within limits.

Regression equation = y = 2012.2x + 1568.9

Slope = 2012.2

LoD = 0.25 µg/mL

LoQ = 0.75 µg/mL

System Suitability Test

The system suitability test was integral chromatographic methods development and carried outnder ICH (Q2) guidelines (20). When HPLC method of is optimized than to check their suitability and stability of the optimized method. The blank (1 injection) injections and standard Molnupiravir (6 injection replicates) were given at a working concentration of 40 µg/mL. The chromatograms obtained by which peak area, retention time, theoretical plates and tailing factor of standard solution were determined and mentioned in Table 6.

Forced Degradation Studies

The degradation is observed with the peak area differences compared to the pre-analyzed solutions of molnupiravir.

Table 3: Precision studies of Molnupiravir standard solution (40 µg/mL)

S. No	*Intraday precision*			*Intermediate precision*	
	10:00	*01:00*	*04:00*	*Day 1*	*Day 2*
1	101.16	101.81	102.08	101.16	101.81
2	101.26	101.72	102.16	101.26	101.72
3	101.84	101.81	102.14	101.84	101.81
4	101.54	101.79	102.86	101.54	101.79
5	101.63	101.7	101.63	101.63	101.7
6	101.69	101.74	101.69	101.69	101.74
Average	101.52	101.76	102.09	101.52	101.76
SD	0.26	0.05	0.44	0.26	0.05
%RSD (Limit NMT 2%)	0.26	0.05	0.43	0.26	0.05

Chromatograms of acidic and oxidative degradation showed extra peaks indicating moderate degradation, i.e., 30.98% degradation in acidic conditions and 89.28% degradation in due to oxidative degradation. Most significant degradation was observed under alkaline conditions, i.e., 91.40%. Molnupiravir was found to be more stable under hydrolytic, thermal & photolytic stress conditions; hence, no degradations were observed. Degradation products formed were well resolved under developed conditions. Under each condition, peak purity of the main peak was found to be 100% as the peak of degradation products were successfully separated and resolved from the main peak of molnupiravir without any interference.

Discussion

The HPLC method is an analytical procedure that is capable of determining the major active pharmaceutical

Table 4: Accuracy data of Molnupiravir

%Level	*Std spiked (Ml)*	*Amount recovered (%)*	*%Recovery*	*Mean %recovery*	*SD*	*%RSD*
100	0	101.18	100.00			
100	0	101.15	99.97	100.00	0.0252	0.0252
100	0	101.20	100.02			
110	4	113.55	102.13			
110	4	113.62	102.20	102.18	0.0442	0.0432
110	4	113.64	102.21			
120	8	123.27	101.72			
120	8	123.66	102.04	101.98	0.2276	0.2232
120	8	123.80	102.16			
130	12	133.75	101.96			
130	12	134.06	101.64	101.85	0.1799	0.1766
130	12	134.08	101.94			

Table 5: Robustness Studies of Molnupiravir

Parameter	*Change in parameter*	*%Estimation*	*Mean*	*SD*	*%RSD*
	240	100.72			
Wavelength (nm)	242	101.20	100.74	0.4503	0.4470
	244	100.30			
	0.8	100.78			
Flow (mL/min)	1.0	101.45	101.34	0.5139	0.5071
	1.2	101.79			
	38	99.94			
Temperature (˚C)	40	100.64	100.12	0.4537	0.4531
	42	99.79			
	55:45	101.14			
Ratio	60:40	101.66	101.22	0.4060	0.4011
	65:35	100.86			

Table 6: System suitability parameters & system precision of molnupiravir

Sr. No.	*Peak area*	*Retention time*	*Theoretical plates*	*Tailing factor*
1	83679.8522	6.017	5062	1.09
2	83871.6277	6.017	5129	1.09
3	83939.1784	6.021	5107	1.09
4	84015.6589	6.025	5074	1.09
5	84083.3777	6.025	5112	1.08
6	84058.2407	6.029	5136	1.07
Average	83941.323	6.022	5103	1.09
S.D.	150.07	0.005	29.6086	0.01
%R.S.D.	0.18	0.080	0.5802	0.77
Limits	NMT 2.0%	NMT 1.0%	NLT 2000	NMT 2.0%

ingredients from different dosage forms. The forced degradation studies help understand the drug's stability during storage conditions. In the present developed method, the drug is eluted at a retention time of 6.0 minutes with good resolution. This developed RP-HPLC method was validated and all validation parameters were found to be within the allowable limit according to ICH guidelines.[17] Although methods have been reported to estimate molnupiravir in pharmaceutical dosage form, no work has been reported on its estimation by RP-HPLC in the capsule dosage form. Therefore, in the present study we have developed and validated the stability indicating RP-HPLC method for molnupiravir in capsule dosage form. The developed HPLC method is simple, specific, accurate, and precise molnupiravir in capsule dosage form. The method was successfully validated in terms of linearity, accuracy, precision, specificity and robustness in accordance with ICH guidelines. The degradation studies

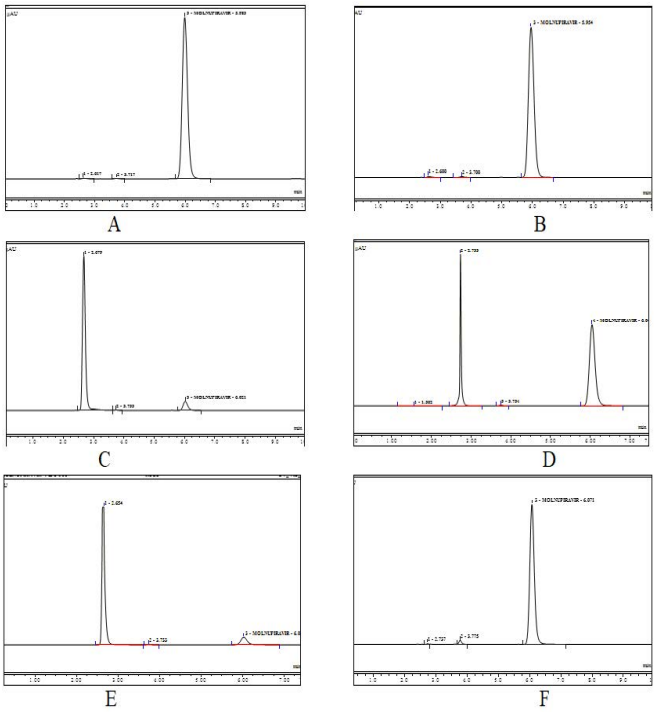

Fig. 5: Forced degradation study of molnupiravir; A) Thermal degradation, B) Photolytic degradation, C) Basic degradation, D) Acidic degradation, E) Oxidative degradation, F) Hydrolytic degradation.

Table 7: Forced degradation studies of molnupiravir

Conditions	*Time (minutes)*	*Temperature (°C)*	*%Residual drug*	*Peak purity index*
Acidic	60	70	69.02	99.99
Basic	15	70	8.59	99.98
Thermal	60	70	99.48	100
Hydrolytic	60	70	99.05	100
Photolytic	24 hrs.	25	98.23	100
Oxidative	30	70	10.71	99.99

were performed with the developed method. Molnupiravir is sensitive to basic, acidic and oxidative conditions. The stability indicating the method is capable of determining molnupiravir in the presence of its degraded products. Here we conclude that the developed method is accurate, stable, sensitive and superior with better system suitability parameters such as theoretical plates and tailing factor. Thus, the described method is suitable for routine analysis and quality control of molnupiravir in the capsule dosage form.

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