COVID DRUG MOLNUPIRAVIR STABILITY INDICATING UV-VISIBLE SPECTRSCOPIC METHOD DEVELOPMENT AND VALIDATION IN BULK AND PHARMACEUTICAL DOSAGE FORM.

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Abstract:
Molnupiravir is an anti-viral medication used in the treatment of COVID-19. Molnupiravir is the first oral antiviral medication. It acts by increasing the frequency of viral RNA mutations and impairs SARS-CoV-2 replication in humans. There are no known serious side effects with Molnupiravir. The World Health Organization has amended its live recommendations for COVID-19 medicines to add a conditional recommendation for the novel antiviral drug Molnupiravir. The COVID-19 treatment recommendation now has included this medication and has a few safety reports. The WHO suggests active medication safety monitoring in addition to other methods of reducing possible risks. This study aims at method development and validation of Molnupiravir in bulk and dosage form by using UV spectroscopy. ELICO SL-210 UV-Visible spectrometer was used in the study. The diluent used for the determination of Molnupiravir is double distilled water. The absorbance maximum was found to be 236nm. The concentration range is 2µg/ml - 40µg/ml. All the validation parameters were carried out according to ICH Guidelines Q2 (R2) which includes Linearity, Precision, Accuracy; Detection Limit, Quantification Limit, Robustness; Specificity and Range are carried out. The results were found to be within the limits as suggested in the ICH guidelines. Stability studies of Molnupiravir were performed according to ICH Q1A and Q1B guidelines. The tests carried out were acid degradation, alkaline degradation, photolytic degradation, oxidative degradation and thermal degradation. The %degradation of the drug Molnupiravir during the degradation studies was found to be within the limits.

Keywords: *Molnupiravir, double distilled water, UV spectroscopy, degradation studies, validation.*

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Introduction:

In 2019, an outbreak of illness originating in China was determined to be caused by a novel virus called SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2). This illness is commonly referred to as COVID-19 or coronavirus disease 2019. The World Health Organization (WHO) officially declared COVID-19 as a pandemic in March 2020. The WHO, along with other public health organizations, is actively monitoring the epidemic and providing information on their respective websites. These organizations have also issued guidance on preventive measures to halt the spread of the COVID-19 virus (Lee C. C et al.).

The virus primarily spreads through respiratory droplets released when an infected person breathes, speaks, sings, coughs, or sneezes. Close proximity to an infected individual may lead to inhalation of these droplets or their entry into the mouth, nose, or eyes. In certain circumstances, airborne transmission can occur when individuals are exposed to tiny droplets or aerosols that remain suspended in the air for extended periods. It is also possible for the virus to spread if a person touches a contaminated surface and subsequently touches their mouth, nose, or eyes, although the risk is minimal (Pourkarim F et al. 2022).

Several COVID-19 vaccines have received emergency use authorization from the U.S. Food and Drug Administration (FDA). Vaccination can help prevent infection or reduce the severity of illness if infection does occur. Furthermore, vaccination against COVID-19 may offer greater protection compared to natural infection. Recent research indicates that individuals previously infected with COVID-19 who are not fully immunized face more than twice the risk of re-infection. Unfortunately, vaccination rates remain low in many low- and middle-income countries. Conversely, oral medications are preferred by some patients due to their ease of administration (Sumardika IW et al. 2021).

Molnupiravir (C13H19N3O7) is an antiviral medication with a molecular weight of 329. 1g/ml. Its IUPAC Name is (2R,3S,4R,5R)-3,4-Dihydroxy-5-[(4Z)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2H)-yl]oxolan-2-yl}methyl 2-methylpropanoate (as given in Fig.1). This antiviral drug, known as molnupiravir or Lagevrio, inhibits the replication of several RNA viruses. It is used to treat individuals with SARS-CoV-2 infection and COVID-19. The medication is taken orally (Imran M et al. 2021).

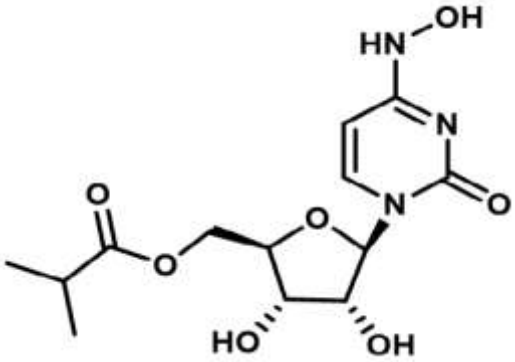

Figure 1: Structure of Molnupiravir

The mechanism of action involves inducing extensive mutations in viral RNA replication through RNA-directed RNA polymerase. By doing so, molnupiravir hinders the spread of viruses. It undergoes conversion into -D-N4-Hydroxycytidine 5′-triphosphate, also referred to as EIDD-1931 5′-triphosphate or NHC-TP. This compound is a ribonucleoside analog that imitates cytidine. Instead of utilizing actual cytidine during replication, the virus's enzyme incorporates NHC-TP into newly synthesized RNA (as given in Fig.2) (Kabinger F et al.2021, Amara A et al.2021, Gordon CJ et al. 2021).

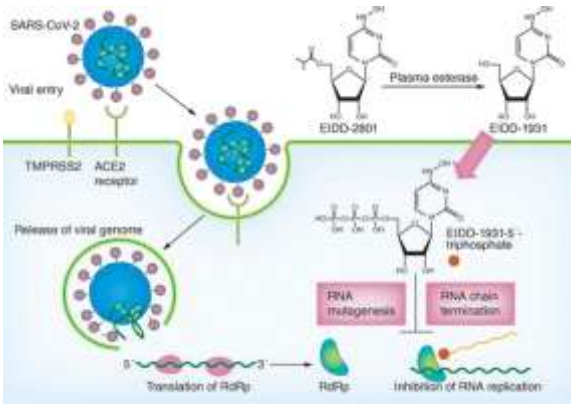

Figure 2: Mechanism of Action of Molnupiravir

Materials and Method:

Chemicals:

Molnupiravir Standarddrug giftedby AUROBINDO, Double distilled water (HPLC Grade), NaOH (AR Grade),HCL, Hydrogen Peroxide.

Instrumentation:

A double beam UV Visible spectrophotometer(ELICO SL-210,Hyderabadand Telangana) equipped with 1cm quartz cuvettes was used. The wavelength range selected for scanning was 200-400nm.

Preparation of Standard Solutions:

Preparation of Standard Stock Solution:

Precisely measured 10mg of Molnupiravir pure drug was placed into a 10ml volumetric flask. The flask was then filled to the mark with diluent to achieve a concentration of 1000µg/ml (stock solution).

Preparation of Standard Working Solutions (100µg/ml solution):

From the aforementioned standard stock solution, 1ml was transferred to a 10ml volumetric flask and diluted with diluent to obtain a concentration of 100µg/ml of Molnupiravir. Serial dilutions were subsequently prepared from the working standard solution.

Preparation of Sample Stock Solution (1000µg/ml solution):

Ten tablets were weighed, and the average weight of each tablet was calculated. The tablets were then powdered, and an amount equivalent to 10mg was placed into a 10ml volumetric flask. Next, 3/4ths of the diluent was added to the flask, followed by sonication for 10 minutes. The solution was filtered and then made up to volume with diluent, resulting in a concentration of 1000µg/ml of Molnupiravir.

Preparation of Sample Working Solution (100µg/ml solution):

From the filtered sample stock solution mentioned above, 1ml was transferred to a 10ml volumetric flask and diluted with diluent to achieve a concentration of 100µg/ml of Molnupiravir.

Selection of solvent:

Based on the solubility of the drug different solvents like methanol, double distilled water were utilized in varying ratios. The suitable solvent was selected as the diluent.

Determination of λmax:

In order to ascertain the wavelength at which Molnupiravir demonstrates maximum absorption (λ max), a standard solution containing 10µg/ml of the drug was subjected to scanning within the range of 200-400 nm, with double distilled water serving as the reference. The analysis revealed that Molnupiravir displayed its highest absorbance at 236 nm.

Method Validation:

1. Specificity/selectivity:

In analytical chemistry, specificity refers to the capability to accurately identify and quantify the substance of interest, even in the presence of other substances that are likely to be present, such as impurities, degradation products, or matrix components. This requires an unambiguous and reliable assessment of the analyte (Jain P et al, 2022).

To assess selectivity, the response of the samples, including the blank and analyte, was measured. It is imperative that no response that could interfere with the analyte's response is detected during this process.

10mg of drug was dissolved in 10ml of the diluent (1000ppm). From the stock solution working standard solution was prepared of concentration 100ppm. 10ppm solution was prepared and

scanned in UV-Visible spectrophotometer at wavelength 200-400nm.Blank and the 10ppm drug solution were scanned.

2. Range

In the field of analytical chemistry, the term "range" pertains to the range of concentrations of a particular substance (known as the analyte) in a sample that can be accurately and precisely measured using a specific analytical method. This range encompasses the lowest and highest concentrations of the analyte that have been validated to produce dependable and consistent results in terms of precision, accuracy, and linearity of the method. The range serves as a significant parameter for assessing the suitability and validity of an analytical procedure for a given application (Jain P et al, 2022).

The absorbances of the prepared serial dilutions were measured using a UV-Visible spectrophotometer. Based on the acquired data, a calibration curve was constructed with absorbance on the y-axis and concentration on the x-axis. The range was determined from this calibration curve.

2.1 Response

2.1.1 Linear response

To validate that the analytical technique is appropriate for the intended application, a linear connection among the concentration of analyte and response should be assessed over the analytical procedure's operating range (Annadi AM et al. 2022).

A least of five concentrations that are evenly dispersed over the range are advised for determining of linearity; however, for more complicated models, more concentrations could be needed.

From the prepared working standard solution of concentration 100ppm serial dilutions from 2µg/ml - 40µg/ml were prepared. All the concentrations are scanned in UV-Visible spectrophotometer and calibration curve was plotted.

2.2Lower Range Limits

The signal-to-noise ratio is determined by comparing measured signals from samples with known low analyte concentrations to those from blank samples. Instead of using blank samples, signals in the appropriate baseline region can be used. The minimum concentrations required for accurate detection or quantification of the analyte is referred to as the detection limit (DL) and quantitation limit (QL) respectively. It is widely agreed among experts that a signal-to-noise ratio of 3:1 is suitable for determining the detection limit, while a ratio of at least 10:1 is considered acceptable for the quantitation limit. These ratios are determined based on the standard deviations of the slope and the linear response (Sharaf YA et al.2022).

DL: The Detection Limit of Molnupiravir was determined according to the standard formula for DL as outlined in the ICH guidelines. This formula incorporates the standard deviation of the response (Y-intercept), denoted as σ and the slope of the calibration curve, denoted as S. The calculated results have been organized in a table.

The expression for the detection limit (DL) is:

$$DL = \frac{3.3\sigma}{S}$$

QL: The Quantitation Limit of Molnupiravir was determined in accordance with ICH guidelines using the standard formula for QL. The formula involves calculating the standard deviation of the response (Y-intercept), denoted as σ, and the slope of the calibration curve, denoted as S. The obtained results have been tabulated.

The expression for the quantitation limit is:

$$QL = \frac{10\sigma}{S}$$

3. Accuracy and Precision

3.1 Accuracy

It is important to establish accuracy for an analytical procedure by testing across the entire range of values that can be reported. This is typically done by comparing the measured results to an expected value. To ensure accuracy, testing should be done under regular conditions of the analytical procedure, which includes testing in the presence of the sample matrix and using the recommended sample preparation steps (Ali SN et al. 2021).

A constant concentration of sample solution (8ppm) was selected and was spiked with 50 %, 100 % &150% of the standard drug solution i.e. 4ppm, 8ppm, 12ppm respectively. Triplicates were measured. The % recovery was calculated following mean recovery was calculated.

3.2 Precision

As part of the validation process for assay and quantitative purity or impurity tests, it is necessary to conduct an assessment of precision. Precision refers to the degree of dispersion observed

between multiple measurements obtained from serial sampling of the same homogenous sample under specific conditions. It serves as a measure of the analytical method's consistency. Precision can be categorized into different degrees, such as repeatability and intermediate precision (BhumikaParmar et al. 2022).

3.2.1 Repeatability

6 measurements at 100% of the test concentration were determined(Deshpande et al. 2023).6 replicates of 20ppm standard solution of Molnupiravir absorbance's was scanned at the optimized wavelength of 236nm.The RSD was calculated from obtained results and tabulated.

$$\%RSD = \frac{Standard\ deviation\ of\ the\ measurement}{Mean\ value\ of\ measurement} \times 100$$

3.2.2 Intermediate Precision

Variations within laboratories are indicated by intermediate precision, which encompasses factors such as different days, analysts, and equipment (Guideline IH, 2005).

Intra Day:

For the intraday assessment, the absorbance of a sample (20µg/ml) was measured at 236nm by different analysts. The Percentage Relative Standard Deviation (%RSD) was calculated and recorded.

Inter Day:

To evaluate interday variability; the absorbance of a sample (20µg/ml) was measured at 236nm on different days. The Percentage Relative Standard Deviation (%RSD) was calculated and documented.

Robustness:

Robustness, a measure of an analytical procedure's ability to remain unaffected by minor intentional changes in method parameters, provides insight into its reliability under typical conditions (Guideline IH, 2022).

To assess robustness, the absorbance of a sample (10µg/ml) was measured at different wavelengths (±1nm), specifically 235nm, 236nm, and 237nm. The concentration selected for this evaluation was 20ppm. Six replicates of the 20ppm concentration were scanned, and the Percentage Relative Standard Deviation (%RSD) was calculated and recorded.

Assay

20 tablets were taken and precisely weighed. It was determined what the tablets average weight was. Then, a mortar and pestle were used to powder the tablets. In a volumetric flask (10ml), weight equal to 10 mg from the tablet label claim was measured and taken. In order to create the sample solution, double distilled water is used as diluent. A 10ppm solution was made from this solution, and the absorbance was measured at 236 nm using a UV-Visible spectrophotometer.
%Assay is calculated by using the formula:

$$\%Assay = \frac{Absorbance\ of\ sample}{Absorbance\ of\ standard} \times \frac{Concentration\ of\ standard}{Concentration\ of\ sample} \times 100$$

Forced Degradation Studies:

Bench top Studies: Standard drug solution of concentration 20ppm was prepared from the stock solution and kept aside. The solution was scanned in uv-visible spectrophotometer at 236nm at 0^{th}hr, 6hrs, 24hrs, 30hrs and 48hrs. From the obtained data %degradation was calculated.

Acid Degradation: 20ppm of drug solutionwas prepared from the stock solution of Molnupiravir.2ml of the 20ppm standard drug solution was taken in a clean 10ml volumetric flask and to it 1ml of prepared 0.1N HCL solution was added. The solution was made up with the diluent and kept aside for 30minutes. The solution was scanned at 0^{th} time and also after 30minutes at 236nm in UV-Visible spectrophotometer. From the obtained absorbances the %degradation of the drug was calculated. The procedure was repeated with 1N HCL and the %degradation was calculated.

Alkaline Degradation: A standard drug concentration of 20ppm was prepared using a stock solution. From the prepared 20ppm solution, 2ml was transferred into a 10ml volumetric flask. Then1ml of 0.1 N NaOH was added to the flask. The solution was diluted to the mark with the diluent and allowed to stand for 20 minutes. The absorbance of the solution was measured at the beginning and after 20 minutes. Using the collected data, the percentage degradation of the drug was calculated. The same procedure was repeated using 1N NaOH, and the percentage degradation was calculated based on the obtained data.

Oxidative Degradation: A standard drug solution with a concentration of 20ppm was prepared. Then, 1ml of 3% hydrogen peroxide was added to the solution, and it was left undisturbed for 30 minutes. The solutions were then analyzed using a UV-visible spectrophotometer, and the percentage degradation was calculated based on the obtained data.

Photolytic Degradation: 20ppm solution was prepared from stock solution and poured into a Petri dish and kept in the UV chamber for 30mins. The absorbance was scanned before and after the exposure of UV rays in the UV-Visible spectrophotometer at 236nm. The %degradation was calculated from the obtained data.

Thermal Degradation: 20ppm of the prepared standard drug solution was poured into a Petri dish and kept in a hot air oven for 10mins at 40°C. The absorbance was scanned before and after the thermal exposure in the UV-Visible spectrophotometer at 236nm. The %degradation was calculated from the obtained data.

Results:

Specificity/Selectivity:

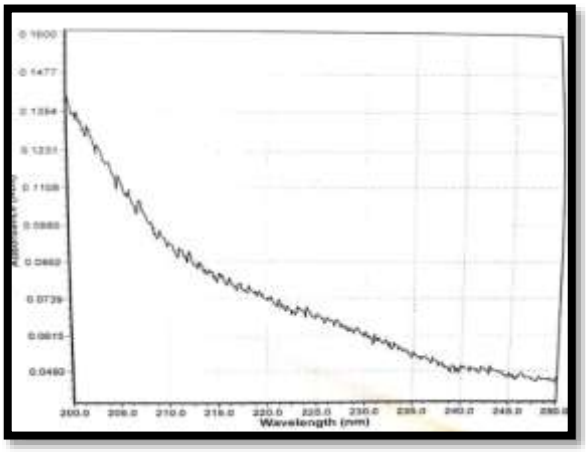

Figure 3: UV Spectra of Blank

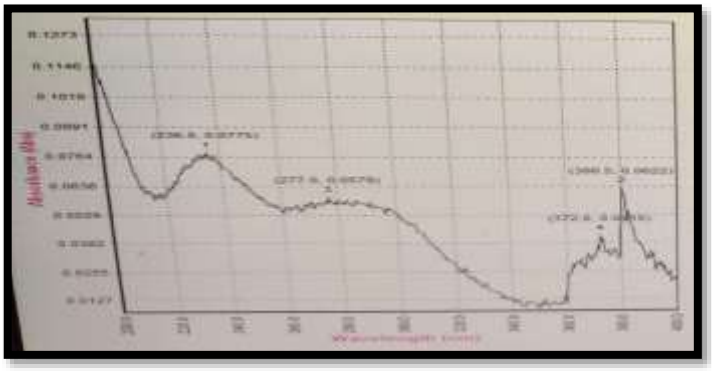

Figure 4: Spectraof Standard Drug Molnupiravir

Inference: The selected lambda max was found to be specific to the drug and no other impurities were found to show the absorbance.

Linear Response:

Table 1: Linearity Data

Concentration	Absorbance
2	0.0123
4	0.1003
6	0.2311
8	0.3987
10	0.5349
12	0.6902
14	0.8381

16	0.991
18	1.125
20	1.3011
22	1.455
24	1.6407
26	1.8001
28	1.9592
30	2.079
32	2.2542
34	2.4296
36	2.5649
38	2.765
40	2.9012

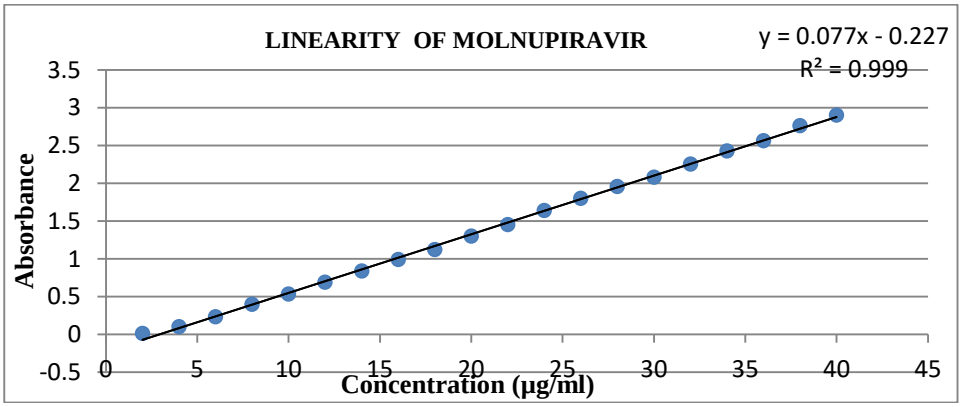

Figure 5: Calibration Curve

Limits: Correlation Coefficient (R2) should be ≥ 0.999.

Result: Correlation Coefficient (r2) for Molnupiravir was 0.999 which was found to be within the limits.

Detection Limit (DL): Detection limit is calculated from the following formula and is found to be:

$$DL = \frac{3.3\sigma}{S} = 0.29787638\mu g/ml$$

Quantitaion Limit(QL): Quantitation limit is calculated from the following formula and is found to be:

$$QL = \frac{10\sigma}{S} = 0.90265571\mu g/ml$$

Accuracy:

Table 2: Accuracy Data

Percentage level	**Absorbance**	**%Recovery**	**Mean % Recovery**
50% (8ppm+4ppm)	0.0989	98.6%	98.57%
	0.0995	99%	
	0.099	98.1%	
100% (8ppm+8ppm)	0.3990	99.8%	99.87%
	0.3984	99.9%	
	0.3986	99.9%	

150% (8ppm+12ppm)	0.6895	99.9 %	99.87%
	0.6897	99.9%	
	0.6903	99.8%	

Limits: % Recovery should be 98-102%

Result: The % Recovery was found to be 98.57%, 99.87% & 99.87% which is within limits.

Precision:

Repeatability:

Table 3: Precision Data

Standard concentration	Absorbance
20ppm	1.3189
20ppm	1.3011
20ppm	1.3017
20ppm	1.3011
20ppm	1.3042
20ppm	1.3017
Mean(x^-)	1.30478333
SD	0.00701097
%RSD	0.53732811

Limits: %RSD should be less than 2.

Result: %RSD was found to be 0.53732811.

Intermediate precision:

Intra Day:

Table 4: Data of Precision by Different Analysts

Concentration	Analyst 1	Analyst 2
20ppm	1.3012	1.4036
20ppm	1.3119	1.4052
20ppm	1.3018	1.4048
20ppm	1.3015	1.4064
20ppm	1.3017	1.4078
20ppm	1.3013	1.4039
Mean	1.30323333	1.405283
SD	0.0042519	0.001585
%RSD	0.32625789	0.112821

Limits: %RSD should be less than 2.

Result: %RSD was found to be within the limits.

Inter Day:

Table 5: Data of Precision on Different Days

Concentration	Day 1	Day 2
20ppm	1.3011	1.4035
20ppm	1.3119	1.4051
20ppm	1.3017	1.4049
20ppm	1.3018	1.4063
20ppm	1.3015	1.4077
20ppm	1.3016	1.4039
Mean	1.30326667	1.405233
SD	0.00423635	0.001558
%RSD	0.32505632	0.110855

Limits: %RSD should be less than 2.

Result: %RSD was found to be within the limits.

Robustness:

Table 6: Robustness Data

Concentration	235nm	236nm	237nm
20ppm	1.2709	1.3189	1.3028
20ppm	1.2726	1.3011	1.3107
20ppm	1.2679	1.3017	1.3175
20ppm	1.2798	1.3011	1.3099
20ppm	1.2654	1.3042	1.3167
20ppm	1.2697	1.3017	1.3064
Mean	1.27105	1.304783	1.310666667
SD	0.00495288	0.007011	0.005723169
%RSD	0.38966822	0.537328	0.436660932

Limits: %RSD should be less than 2. **Result:** %RSD was found to be within the limits.

Assay:

Table 7: Assay Data

Sample Absorbance	1.2989
Standard Absorbance	1.3011
Standard Concentration	20
Sample Concentration	19.9661825

%Assay is calculated by using the formula:

$$\%Assay = \frac{Absorbance\ of\ Sample}{Absorbance\ of\ Standard} \times \frac{Concentration\ of\ Standard}{Concentration\ of\ Sample} \times 100$$

= 99.6%

Forced Degradation Studies:

Table 8: Data of Forced Degradation Studies

Type	Condition	% Degradation
Alkali	0.1N NaOH	10.50%
	1NNaOH	14.50%
Acidic	0.1N HCL	10.00%
	1N HCL	13.05%
Oxidative	3% H2O2	12.00%
Photolytic	UV Chamber	5.00%
Thermal	40°c	10.75%
Bench top	6hrs	0.25%
	24hrs	1.00%
	30hrs	1.50%
	48hrs	2.00%

Limits: % Degradation should be < 20%. **Result:** The %Degradation was found to be less than 20% which is within limits.

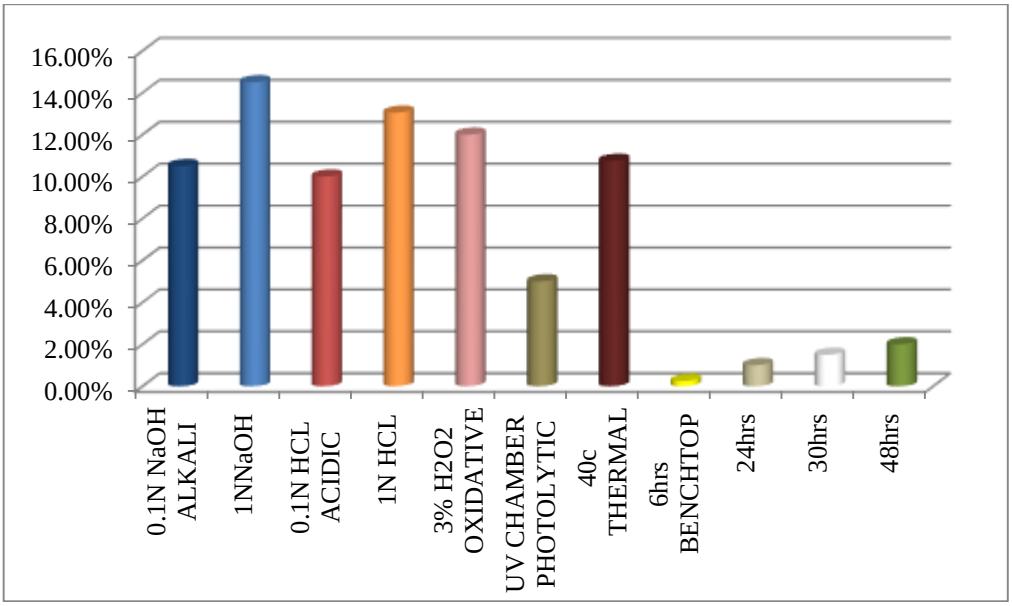

Figure 6: Graphical Representation of % Degradation

Discussion:

Specificity: Blank and the standard drug concentration solutions were scanned in the UV-Visible spectrophotometer. The lambda max specific to the drug was 236nm.The selected lambda max was found to be specific to the drug and no other impurities were found to show the absorbance.

Range: The concentration range was found to be 2µg/ml - 40µg/ml.

Linear Response: The UV-Visible spectrophotometer was used to scan all the dilutions, and the resulting values were recorded in a table. A calibration curve was then plotted using the concentration as the x-axis and the absorbance as the y-axis, based on the obtained absorbance data. The resulting curve demonstrated linearity, with an r^2 value of 0.99, which falls within the limits specified in the ICH guidelines. The response observed was found to be linear.
The detection limit was 0.29787638µg/ml and the quantification limit was found to be 0.90265571µg/ml.

Accuracy: The standard drug concentration selected for the study was 4ppm, 8ppm and 12ppm and the sample concentration was 8ppm. The sample solution was spiked with the standard drug solution. The % Recovery was found to be 98.57%, 99.87% & 99.87% which is within limits as per ICH guidelines.

Repeatability: 20ppm was selected for the study of precision. Mean and SD were calculated from the obtained data. %RSD was found to be 0.53732811.

Intraday: Intraday precision was carried out on a same day with different analysts. The absorbance of 20ppm solution was scanned in the UV-Visible spectrophotometer and the mean and standard deviation were calculated. %RSD was found to be within the limits i.e. less than 2.

Inter day: Inter dayprecision was carried out in a different day. Mean and standard deviation of the obtained data was calculated. %RSD was found to be within the limits i.e. less than 2.

Robustness: Robustness was carried out by having a difference in the wavelength of ±1nm. From the obtained data mean, SD and %RSD were calculated and tabulated. The %RSD at the three wavelengths is compared. %RSD was found to be within the limits i.e. less than 2.

Assay: The assay result was found to be 99.6%.

Forced Degradation Studies: The forced degradation studies carried out were bench top, alkaline degradation, acid degradation, oxidative, photolytic and thermal degradation. The % degradation was calculated from the obtained data and is tabulated. The graph of the data is shown.

Conclusion:

The development and validation of the Molnupiravir drug using UV spectroscopy were conducted, resulting in an accurate, simple, precise, sensitive, and cost-effective method. The quantification method for Molnupiravir was

specifically developed for tablet formulation. All validation parameters have shown improvement compared to previous work. Furthermore, all results obtained were found to be within the limits specified by the ICH guidelines. Therefore, the proposed method can be utilized for the validation of Molnupiravir.

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