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Original Article

Drug-Excipients Compatibility Studies of Molnupiravir in an Attempt of Developing a Stable Molnupiravir Capsule Formulation for the Treatment of COVID-19

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ABSTRACT

Background: Molnupiravir is an antiviral medication primarily used for the treatment of COVID-19. Clinical trials have shown that molnupiravir reduces the risk of hospitalization and death due to COVID- 19 when taken early in the course of infection. The USFDA had granted an EUA (emergency use authorization) in December 2021 for molnupiravir to treat COVID-19. Many other countries have also authorized its use under emergency provisions. The current research focuses on performing Drug-Excipients Compatibility Studies of Molnupiravir in an attempt of developing a Stable Molnupiravir Capsule formulation-200 mg. **Materials and Methods:** Compatibility of various excipients with Molnupiravir API was studied. Drug and individual excipients were mixed in 1:1 ratio and filled in USP Type I transparent glass vials. Samples were tested at initial, 15 days, 30 days for Description, Assay and Related substances. Appropriate excipients were chosen based on the results obtained. With the selected excipients 3 different capsule formulations were prepared by varying the excipients quantities and were studied for Assay, Related Substances and Dissolution profile for determining the best suitable formula. **Results:** Among three different formulations manufactured, The Assay, Related Substances and Dissolution profile of Formulation 3 was found satisfactory. **Conclusion:** Formulation 3 was found to be the best suitable formula and was considered for formulating Molnupiravir 200 mg Capsules and for further studies.

Keywords: Antiviral, COVID-19, Drug-Excipients Compatibility Studies, Emergency Use Authorization, Molnupiravir.

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INTRODUCTION

Coronavirus Disease 2019 (COVID-19), caused by the Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), has emerged as one of the most devastating global public health crises of the 21st century. Since its identification in late 2019, the disease has resulted in millions of infections and deaths worldwide, exerting unprecedented pressure on healthcare systems, economies, and social structures. The rapid transmission, emergence of viral variants, and varying clinical severity-from asymptomatic infection to severe respiratory failure-have necessitated urgent therapeutic and preventive interventions.

In response to the pandemic, several vaccines were developed and deployed at an accelerated pace under Emergency Use Authorization (EUA) to reduce disease severity and mortality. While vaccination has proven effective in decreasing hospitalization and death rates, it does not completely prevent infection, reinfection, or viral transmission, particularly in vulnerable populations such as the elderly, immunocompromised individuals, and those with comorbidities. Moreover, global inequities in vaccine access and vaccine hesitancy have further underscored the need for effective therapeutic options.

Although various therapeutic agents, including monoclonal antibodies and antiviral drugs, have been investigated for COVID-19 treatment, many of these therapies require intravenous administration in hospital or controlled clinical settings. This limitation significantly restricts their widespread use, particularly during early-stage infection when antiviral intervention is most effective. Therefore, the development of safe, efficacious, and easily administered oral antiviral medications has been recognized as a critical strategy for reducing disease progression, hospital burden, and mortality.[1]

Molnupiravir is an oral prodrug that turns into β-D-N4-Hydroxycytidine (NHC) in the body. It exhibits

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broad-spectrum antiviral activity against a range of RNA viruses, including influenza viruses, Ebola virus, and coronaviruses. Molnupiravir exerts its antiviral effect by inducing viral error catastrophe through incorporation into viral RNA, leading to the accumulation of deleterious mutations and inhibition of viral replication.

Monupiravir drug substance is White to Off-white solid. It is soluble in water and has Specific optic rotation of between -16° to -24°. The chemical structure of molnupiravir is shown in Figure 1. Preclinical studies demonstrated its potent antiviral activity against SARS-CoV-2, prompting rapid progression into clinical trials. Clinical studies have shown that early administration of molnupiravir significantly reduces viral load, risk of hospitalization, and mortality in patients with mild to moderate COVID-19,[2] particularly when administered within the first few days of symptom onset. Based on these findings, the United States Food and Drug Administration (USFDA) granted Emergency Use Authorization to molnupiravir in December 2021 for the treatment of COVID-19 in adults at high risk of disease progression. Subsequently, regulatory authorities in several other countries approved its use under emergency or conditional authorization pathways.

As an oral antiviral agent intended for outpatient use, molnupiravir is commonly formulated as capsules. However, the successful therapeutic performance of an oral solid dosage form depends not only on the Active Pharmaceutical Ingredient (API) but also on the selection of appropriate excipients. Excipients play a crucial role in ensuring the stability, bioavailability, manufacturability, and overall quality of the final pharmaceutical product. Incompatibility between the drug substance and excipients can lead to physical or chemical degradation, reduced potency, altered dissolution behavior, and compromised shelf life.[3]

Drug-excipient interactions are particularly critical for nucleoside analogs such as molnupiravir, which may be sensitive to factors such as moisture, temperature, pH, and oxidative conditions. Previous studies on antiviral formulations have highlighted that inappropriate excipient selection can adversely affect drug stability and performance. Therefore, comprehensive drug-excipient compatibility studies are an essential prerequisite in the formulation development of a stable and effective capsule dosage form.

Despite the clinical importance and widespread emergency use of molnupiravir, limited published literature is available on its preformulation characteristics and systematic drug-excipient compatibility studies, particularly in the context of capsule formulation development. Most existing studies primarily focus on clinical efficacy, pharmacokinetics, and safety, with comparatively little emphasis on formulation challenges, stability considerations, and excipient selection. Additionally, there is a lack of detailed experimental data addressing the physicochemical interactions between molnupiravir and commonly used pharmaceutical excipients under various stress conditions.[4]

This gap in formulation-based research presents a significant challenge in developing a robust, stable, and commercially viable oral dosage form of molnupiravir that meets regulatory and quality requirements.

The current research focuses on performing Drug-Excipients Compatibility Studies of Molnupiravir in an attempt of developing Stable Molnupiravir Capsule formulation-200 mg.

MATERIALS AND METHODS

Chemicals and Reagents

Molnupiravir Active Pharmaceutical Ingredient (API) was used as the model antiviral drug for the present investigation. Pharmaceutical-grade excipients commonly employed in solid oral dosage forms were selected for compatibility and formulation studies. These included microcrystalline cellulose, lactose, maize starch, pregelatinized starch, croscarmellose sodium, crospovidone, talc, colloidal silicon dioxide, magnesium stearate, and sodium lauryl sulphate. All excipients were of compendial grade and were used as received without further purification.[5]

Instruments and Analytical Equipment

The analytical and evaluation studies were carried out using the following instruments:

- UV-Visible spectrophotometer for preliminary analysis.
- Fourier Transform Infrared (FTIR) spectrophotometer for compatibility assessment.
- Reverse Phase High Performance Liquid Chromatography (RP-HPLC) system for assay and related substances analysis.
- Dissolution testing apparatus (USP Type I - Basket) for *in vitro* drug release studies.

All instruments were calibrated prior to use in accordance with standard laboratory procedures.

Drug-Excipient Compatibility Studies

The development of a stable oral capsule formulation requires careful selection of excipients that are physically and chemically compatible with the active pharmaceutical ingredient. Therefore, drug-excipient compatibility studies were carried out as a preliminary step in the formulation development of Molnupiravir Capsules 200 mg.[6]

Based on their functional roles in capsule formulations, various excipients such as diluents, disintegrants, lubricants, and surfactants were identified and selected for compatibility testing.

The selected excipients, along with their pharmaceutical category and quantities, are listed in Table 1.

For the compatibility study, molnupiravir API was individually mixed with each excipient in a 1:1 (w/w) ratio, as this ratio represents a worst-case scenario and helps in detecting potential interactions. The API and each Excipient mixtures were thoroughly blended to ensure uniformity and then transferred into USP Type I transparent glass vials.[7]

Two storage conditions were employed to evaluate the influence of environmental exposure:

- Closed vials: Vials sealed with rubber stoppers and aluminum seals.
- Open vials: Vials left unsealed, without rubber stoppers or aluminum seals.

The prepared samples were stored under controlled conditions and evaluated at initial, 15-day, and 30-day intervals. At each time point, the samples were checked for:

- Physical description (color change, agglomeration, or any visible instability).
- Assay of molnupiravir.
- Related substances to detect any degradation products.

The compatibility of molnupiravir with each excipient was determined based on the absence of significant physical changes, acceptable assay values, and no appreciable increase in related substances.[8]

Selection of Excipients for Capsule Formulation

Based on the results obtained from the drug-excipient compatibility studies, excipients that demonstrated acceptable compatibility with molnupiravir were shortlisted for further formulation development. The compatible excipients, their functional roles, and manufacturer details are summarized in Table 2. These excipients were selected to ensure optimal flow properties, content uniformity, stability, and dissolution performance of the final capsule formulation.[9]

Development of Molnupiravir Capsule Formulations

Using the selected compatible excipients, three different capsule formulations (F1, F2, and F3) were designed for Molnupiravir Capsules 200 mg. The formulations were developed by varying the quantities of excipients while maintaining a constant drug content of 200 mg per capsule, in order to study the effect of excipient concentration on formulation performance.

The quantitative composition of each formulation is presented in Table 3. For each formulation, a batch size of 100 capsules was prepared.[10]

The accurately weighed quantities of molnupiravir API and excipients were blended uniformly to ensure homogeneity. Lubricants such as magnesium stearate and talc were added to minimize friction during capsule filling. Colloidal silicon dioxide was incorporated to improve flow characteristics of the blend.

The final blends were filled into hard gelatin capsules of size "2" with white opaque body and white opaque caps using a capsule-filling machine.

Evaluation of Capsule Formulations

The prepared capsule formulations were evaluated for critical quality attributes, including:

- Assay.
- Related substances.

Table 1: Excipients identified and selected for Drug Excipients Compatibility studies.

Sl. No.	Name of Excipient	Pharmaceutical category	Drug to Excipient Ratio	API + Excipient Quantity (mg)
1	Molnupiravir	Active	NA	
2	Microcrystalline Cellulose	Diluent	1:1	100+100=200
3	Lactose	Diluent	1:1	100+100=200
4	Maize Starch	Diluent	1:1	100+100=200
5	Pregelatinized Starch	Disintegrant	1:1	100+100=200
6	Croscarmellose Sodium	Disintegrant	1:1	100+100=200
7	Crospovidone	Disintegrant	1:1	100+100=200
8	Talc	Lubricant	1:1	100+100=200
9	Colloidal Silicon Dioxide	Lubricant	1:1	100+100=200
10	Magnesium Stearate	Lubricant	1:1	100+100=200
11	Sodium Lauryl Sulphate	Surfactant	1:1	100+100=200

Table 2: Excipients that were found suitable for formulation of Molnupiravir Capsules 200 mg.

Sl. No.	Ingredients	Function	Manufacturer
1	Molnupiravir	Active pharmaceutical ingredient	Century
2	Microcrystalline Cellulose PH 102	Diluent	NB Enterprises
3	Lactose Monohydrate	Diluent	Saputo Dairy
4	Pregelatinized Starch	Disintegrant	Universal Starch Chem Allied Ltd.,
5	Colloidal Silicon Dioxide	Lubricant	Boa-inky Pharma Ltd.,
6	Talc	Lubricant	Neelkanth Minechem
7	Magnesium Stearate	Lubricant	Prachin Chemicals
8	Hard gelatin capsule size "2" White opaque body/ White opaque caps	Capsule	Biopharma capsules

Table 3: Formulation composition of the trials.

Sl. No.	Ingredients	Quantity/capsule (mg)		
		F1	F2	F3
1	Molnupiravir	200	200	200
2	Microcrystalline Cellulose PH 102	15	10	10
3	Lactose Monohydrate	30	20	15
4	Pregelatinized Starch	15	15	12
5	Colloidal Silicon Dioxide	3	1.5	1.5
6	Talc	2	1.5	1.5
7	Magnesium Stearate	2	2	2
	Formula Weight	267	250	242
8	Hard gelatin capsule size "2" White opaque body/ White opaque caps	1No	1No	1No

- *In vitro* dissolution.

The dissolution studies were carried out using a USP Type I (basket) dissolution apparatus to assess the drug release characteristics of each formulation. Based on the comparative evaluation of assay values, impurity profile, and dissolution performance, the most suitable formulation was identified.

RESULTS

The finalized composition of the optimized formulation is presented in Table 4.

DISCUSSION

The current study was undertaken to evaluate the compatibility of various pharmaceutical excipients with Molnupiravir API and to develop a stable and effective capsule formulation of Molnupiravir 200 mg. Compatibility between the drug and excipients plays a crucial role in ensuring chemical stability, therapeutic efficacy, manufacturability, and shelf-life of solid dosage forms. Any undesirable interaction may result in degradation, altered dissolution behaviour, or compromised product quality.

Drug-excipient compatibility studies performed through physical observation, assay, and related substances analysis revealed that the selected excipients did not induce adverse interactions with Molnupiravir. The absence of significant color change, physical instability, and desirable assay and impurity profile indicated satisfactory compatibility.

Following compatibility screening, three trial formulations were developed by varying excipient concentrations while maintaining constant API strength. Comparative evaluation of their performance parameters indicated that Formulation 3 provided better stability and dissolution efficiency. The optimized levels of microcrystalline cellulose, lactose monohydrate, and pregelatinized starch helped achieve desirable capsule integrity, disintegration characteristics, and drug release. Lubricants and glidants effectively improved flowability and ensured uniform capsule filling.

The findings of this study highlight the importance of rational excipient selection and optimization during formulation development. The successful identification of a stable Molnupiravir capsule formulation supports its further development toward large-scale manufacturing and regulatory evaluation.

Table 4: Finalized formula.

Sl. No.	Ingredients	Quantity/capsule (mg)	Function	Manufacturer
1	Molnupiravir	200	Active pharmaceutical ingredient	Century
2	Microcrystalline Cellulose PH 102	10	Diluent	NB Enterprises
3	Lactose Monohydrate	15	Diluent	Saputo Dairy
4	Pregelatinized Starch	12	Disintegrant	Universal Starch Chem Allied Ltd
5	Colloidal Silicon Dioxide	1.5	Lubricant	Boa-inky Pharma Ltd
6	Talc	1.5	Lubricant	Neelkanth Minechem
7	Magnesium Stearate	2	Lubricant	Prachin Chemicals
8	Hard gelatin capsule size "2" White opaque body/ White opaque caps	1 No	Capsule	Biopharma capsules
Capsule Weight		Around 242 mg		

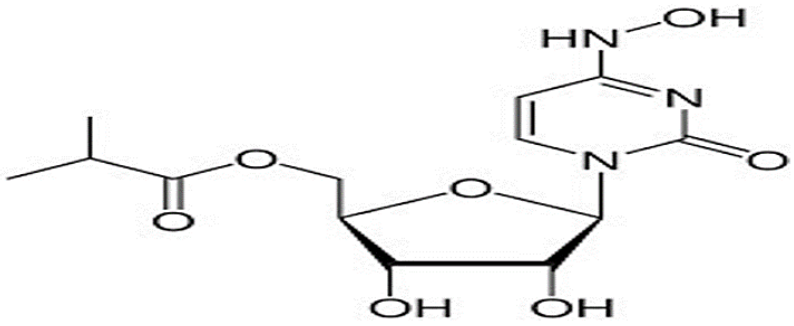

Figure 1: Chemical Structure of Molnupiravir.

CONCLUSION

The present study successfully demonstrated the importance of systematic drug-excipient compatibility assessment in the formulation development of Molnupiravir Capsules 200 mg. Compatibility studies confirmed that Molnupiravir exhibited satisfactory stability with the selected pharmaceutical excipients under the tested storage and study conditions. Based on the compatibility outcomes, three formulations were developed and comparatively evaluated.

Among the three trials, Formulation 3 (F3) showed superior characteristics with respect to assay consistency, and an acceptable related substances and dissolution profile, indicating better physicochemical stability and pharmaceutical suitability. Therefore, Formulation 3 was finalized as the optimized and promising formulation for the development of Molnupiravir 200 mg capsules.

This study provides a scientific foundation for further large-scale manufacturing, extended stability studies, regulatory submission, and potential commercial development of a stable oral Molnupiravir capsule dosage form intended for effective COVID-19 management.

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ABBREVIATIONS

USFDA: United States Food and Drug Administration; **EUA:** Emergency Use Authorization; **API:** Active Pharmaceutical Ingredient; **USP:** United States Pharmacopeia; **UV:** Ultraviolet Visible; **FTIR:** Fourier Transform Infrared Spectroscopy; **RP-HPLC:** Reverse Phase High Performance Liquid Chromatography; **HPLC:** High Performance Liquid Chromatography; **mg:** Milligram; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus 2.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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SUMMARY

The present research work was focused on performing systematic drug-excipient compatibility studies of Molnupiravir with the objective of developing a stable Molnupiravir Capsule 200 mg formulation. Molnupiravir API was individually mixed with selected pharmaceutical excipients in a 1:1 ratio and stored in USP Type I glass vials under closed and open conditions. Samples were evaluated at initial, 15-day, and 30-day intervals for physical description, assay, and related substances.

Based on the compatibility outcomes, suitable excipients were selected for formulation development. Three capsule formulations were prepared using compatible excipients with varying quantities and evaluated for assay, related substances, and dissolution characteristics. Comparative assessment revealed that Formulation 3 exhibited optimum performance, demonstrating acceptable stability and drug release behaviour.

Therefore, Formulation 3 was finalized as the most suitable composition for the development of Molnupiravir 200 mg capsules, providing a promising basis for further formulation development, large-scale production, and extended stability investigation.

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