Formulation and Evaluation of Nirmatrelvir Sublingual Tablet Used for COVID-19 Treatment

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ABSTRACT

Introduction: Nirmatrelvir, an antiviral agent used in the management of COVID-19, exhibits reduced systemic bioavailability when administered orally due to extensive hepatic first-pass metabolism. **Aim:** To formulate and evaluate Nirmatrelvir sublingual tablets to enhance bioavailability and achieve rapid disintegration for immediate therapeutic action. **Objectives:** To prepare sublingual tablets using direct compression; assess pre-compression properties; evaluate post-compression, to study in vitro permeation; and to confirm drug – excipient compatibility using FTIR. **Results:** The powder blend showed good flow properties. All post-compression parameters complied with pharmacopeial limits, indicating satisfactory mechanical strength and uniformity. The optimised formulation demonstrated rapid wetting and disintegration, leading to significantly enhanced dissolution. In vitro permeation studies indicated improved transmucosal absorption of Nirmatrelvir. FT-IR analysis confirmed the absence of significant interactions between the drug and excipients. **Summary:** The direct compression technique successfully produced fast-disintegrating Nirmatrelvir sublingual tablets with desirable physicochemical and biopharmaceutical properties. Improved dissolution and permeation suggest greater therapeutic efficiency. **Conclusion:** Nirmatrelvir sublingual tablets developed in this study effectively address limitations of oral administration by providing faster onset of action and improved bioavailability. This dosage form presents a promising approach for rapid antiviral therapy, especially in emergency or acute clinical conditions.

KEY WORDS

Nirmatrelvir, Sublingual tablet, Anti-viral, FTIR analysis, In vitro permeation, emergency use.

1.INTRODUCTION

A novel coronavirus disease caused by SARS-COV-2 (Severe Acute Respiratory Syndrome Coronavirus-2) was first reported in China. On January 30, 2020, the World Health Organisation (WHO) declared the novel coronavirus outbreak a Public Health Emergency of International Concern. Subsequently, on February 11, the WHO officially named the disease "Coronavirus Disease 2019" (COVID-19) [1]. In India, the first case of COVID-19 was reported on January 27, 2020, in the state of Kerala [2].

2. DEFINITION:

A coronavirus gets its name from the way it looks under a microscope. The word “corona” means “crown,” and when examined closely, the round virus has a “crown” of proteins called peplomers, which are also known as spike proteins, jutting out from its centre in every direction [4].

Figure 1: Coronavirus

3. VIROLOGY AND EPIDEMIOLOGY

A human coronavirus was first isolated in 1965 from the nasal secretions of a male child with the common cold by Tyrell and Bynoe. Due to its crown-like appearance under an electron microscope, resembling the solar corona, the virus was named 'coronavirus.' Such appearance is because of the spike [S] glycoprotein radiating from the viral surface. A coronavirus contains four structural proteins, including spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins. Coronaviruses are classified into four subfamilies: alpha, beta, gamma, and delta [5].

4. SYMPTOMS [2]:

The most common symptoms of COVID-19 are

- Fever
- Dry cough
- Loss of taste or smell
- Sore throat
- Shortness of breath

5. THERAPEUTIC APPROACHES:

- **Antiviral Therapy**
  1) Remdesivir [8]
  2) Nirmatrelvir–Ritonavir (Paxlovid) [8]
  3) Molnupiravir [9]
- **Immunomodulators**
  1) Baricitinib (JAK Inhibitor)
  2) Tocilizumab (IL-6 Inhibitor) [38]
- **Cell Therapy**
  1) T cell therapy
  2) Mesenchymal Stem Cell (MSC) Therapy

6. MODES OF TRANSMISSION [10]

a. Respiratory transmission: respiratory droplets and aerosols
b. Fomite Transmission
c. SARS-CoV-2 in Saliva
d. UV Light's Effectiveness against Coronaviruses
e. pH Impact on Coronavirus Viability

7. CAUSATIVE AGENT [11]

The causative agent of COVID-19 is Severe Acute Respiratory Syndrome Coronavirus 2, commonly referred to as SARS-CoV-2.

8. INCUBATION PERIOD [12]

The incubation period of COVID-19 varies depending on the variant and individual factors. Average incubation period: 5-6 days, with symptoms typically appearing within 2-14 days after exposure.

9. DIAGNOSTIC METHOD [4]

The World Health Organisation (WHO) and the U.S. Food and Drug Administration (FDA) recommend two main categories of diagnostic techniques for detecting SARS-CoV-2 infection:

- Nucleic acid amplification tests (NAATs)
- Serological tests for viral antigens

The other tests include chest x-rays or CT scans [8].

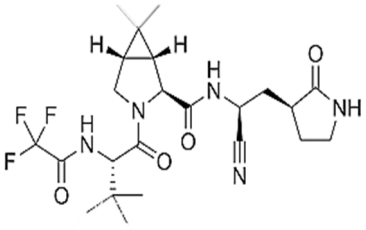
10. PREVENTION [2]

Preventive measures remained the primary strategy to limit the spread of infections. Early screening, timely diagnosis, patient isolation, and appropriate treatment were essential to control further transmission.

11. DRUG PROFILE [13]

Generic Name: Nirmatrelvir
Category: Antiviral
Synonyms:(1R,2S,5S)-N-((S)-1-Cyano-2-((S)-2-oxopyrrolidin-3-yl)ethyl)-3-((S)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl)-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide; 3-Azabicyclo[3.1.0]hexane-2-carboxamide, N-[(1S)-1-cyano-2-[(3S)-2-oxo-3-pyrrolidinyl]ethyl]-3-[(2S)-3,3-dimethyl-1-oxo-2-[(2,2,2-trifluoroacetyl)amino]butyl]-6,6-dimethyl-, (1R,2S,5S);
Chemical Name : (1R,2S,5S)-N-[(1S)-1-cyano-2-[(3S)-2-oxopyrrolidin-3-yl]ethyl]-3-[(2S)-3,3-dimethyl-2-[(2,2,2-trifluoroacetyl)amino]butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

Molecular Formula: $C_{23}H_{32}F_3N_5O_4$
Molecular Weight: 499.54 g/mol
Structure:



pH: Both alkaline and acid hydrolysis
pKa ≈ 10.26
PHYSICAL CHARACTERISTICS
Form: Powder

Colour: White to off-white
Solubility: Sparingly soluble in ethanol, soluble in acetonitrile, and slightly soluble in isopropyl alcohol.
Melting Point ≈ 192.9 °C (379.2 °F)
Dosage Forms: Tablet
Strengths: 150 mg

Mechanism of Action

Nirmatrelvir is an inhibitor of a cysteine residue in the 3C-like protease (3CLPRO) of SARS-CoV-2. This cysteine is responsible for the activity of the 3CLPRO of SARS-CoV-2 and potentially other members of the coronavirus family. The 3CLPRO, also known as the main protease or non-structural protein 5, is responsible for cleaving polyproteins 1a and 1ab. Without the activity of the 3CLPRO, non-structural proteins (including proteases) cannot be released to perform their functions, inhibiting viral replication.

Pharmacokinetic Parameter

C_{max} (µg/mL) **:** 3.39(1.93, 5.40)
AUC_{tau} (µg/mL) **:** 28.3(12.5, 52.5)
C_{min} (µg/mL) **:** 1.40(0.48, 3.45)
$t_{1/2(h)}$ **:** 2.02 ± 0.55
T_{max}(h) **:** 0.63(0.55-1.50)
Cl/F **:** 66.83(43)
Metabolism **:** Minimal, primarily metabolised by CYP3A4
Protein binding ≈ 69%
Excretion **:** Primarily renal
Distribution **:** Not known whether nirmatrelvir is distributed into human or animal milk.

Indications and Usage for Nirmatrelvir

Nirmatrelvir is indicated for the treatment of mild-to-moderate coronavirus disease 2019 (COVID-19) in adults who are at high risk for progression to severe COVID-19, including hospitalisation or death.

Contraindications

History of clinically significant hypersensitivity reactions to the active ingredient (nirmatrelvir) or any other components.

Drug Interactions

Nirmatrelvir can alter the plasma concentrations of other drugs, and other drugs may alter the plasma concentrations of Nirmatrelvir.

Adverse Reactions/Side Effects

Most common adverse reactions (incidence ≥1% and greater incidence than in the placebo group) are dysgeusia and diarrhoea.

Limitations of Use

Nirmatrelvir is not approved for use as pre-exposure or post-exposure prophylaxis for prevention of COVID-19.

Therapeutic use

Used to treat mild to moderate COVID-19.

Warnings and Precautions

Hypersensitivity Reactions: Anaphylaxis, serious skin reactions (including toxic epidermal necrolysis and Stevens-Johnson syndrome), and other hypersensitivity reactions have been reported with nirmatrelvir. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue and initiate appropriate medications and/or supportive care.

Storage and Handling

Store at USP controlled room temperature 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C to 30°C (59°F to 86°F).

12. MATERIAL AND METHODOLOGY

Table 1: List of Materials

S.NO	MATERIALS NAME	MANUFACTURE NAME	USES
1.	Nirmatrelvir	Virchow Laboratories Limited,Hyderbad	API
2.	Sodium starch glycolate	Maithri Drug Private Limited,Telangana.	Super disintegrant
3.	Mannitol	Maithri Drug Private Limited,Telangana.	Diluent, Filler, Sweetening Agent
4.	Pre-gelatinised starch	Maithri Drug Private Limited,Telangana.	Binder, Disintegrant, Filler, Stabilizer
5.	Magnesium stearate	Maithri Drug Private Limited,Telangana.	Lubricant, Anti-adherent, Glidant
6.	Polyvinyl pyrolidone	Maithri Drug Private Limited,Telangana.	Binding Agent, Solubilizing Agent, Stabilizer, Film Former, Disintegrant
7.	Crospovidone	Maithri Drug Private Limited,Telangana.	Super disintegrant

13. METHODOLOGY

Dose Calculation

Formula:

Sublingual Dose = Oral Dose × Oral Bioavailability / Sublingual Bioavailability

Oral Dose = 150mg

Oral Bioavailability = <10%

Sublingual Bioavailability = 100%

Sublingual Dose = 150 × 10 / 100 = 15 mg

Direct Compression Method

This is one of the most commonly used methods in the commercial manufacturing of sublingual tablets due to its simplicity, cost-effectiveness and efficiency. It involves blending compatible ingredients without the need for additional granulation steps prior to lubrication and compression. This method provides good mechanical strength and promotes rapid disintegration. The formulation typically includes fast-soluble superdisintegrants, binders, lubricants, dried binders, surface- active agents, artificial sweeteners and flavouring agents. Sugar-based excipients are widely used as bulking agents because of their high-water solubility, pleasant taste, and favourable mouth feel.

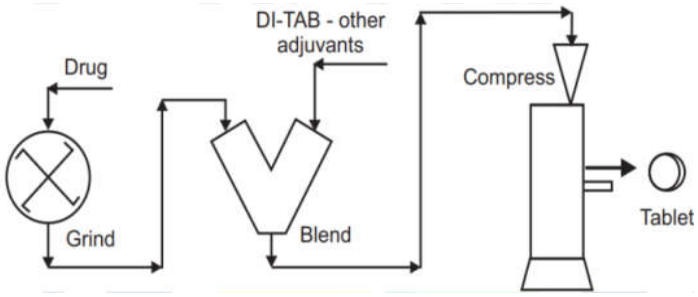


Figure 2: Formulation of Sublingual Tablet

Table 2: Formulation table of Nirmatrelvir

FORMULATION CODE	DRUG (mg)	PVP (mg)	MANNITOL (mg)	PRE-GELATINSED STRACH (mg)	SSG (mg)	CROSPOVIDONE (mg)	MAGNESIUM STREARATE (mg)
F_1	15	5	6.25	3.75	4.75	4.75	0.5

14. EVALUATION PARAMETER

A) Pre-Compression Studies [17, 18, 19]

Organoleptic Evaluation

The investigation and documentation of the drug's organoleptic features, including colour, odour, look and scent, was done through visual examination. (Table 3)

Angle of Repose

The angle of repose was determined using the funnel method. (Table 3)

Bulk Density

A precisely weighed amount of powder was passed through a #60 sieve and transferred to a measuring cylinder. (Table 3)

Tapped Density

After measuring bulk density, the cylinder was tapped 100 times to allow powder settling, and the final volume was recorded. (Table 3)

Carr's Index

Carr's index was calculated to assess compressibility. (Table 3)

Hausner's Ratio

Hausner's ratio was used to evaluate flowability. (Table 3)

Determination of Solubility

To ascertain the soluble nature of Nirmatrelvir, a specific amount of medication (about 1 - 2mg) was placed in a different test tube, amd 5mL of the solvent (water,acetone, pH 5.5) was added, give it a good shake for several minutes. Keep tract of the medication's solubility. (Table 3)

Table 3: Evaluation parameter of pre-compression studies

Test Parameter	Batch F1
Colour	White Crystalline Power
Odour	Odourless
Angle of Repose	27.85
Bulk Density	0.7
Tapped Density	0.9
Carr's Index	22.2
Hausner's Ratio	1.29
Water	Partically insoluble
Ether	Partically insoluble
Chloroform	Partically insoluble
Acetone	Freely soluble
Dil.NaoH	Freely soluble
Alcohol	Sparingly soluble

Determination of Lambda(λ)Max of Nirmatrelvir

Initially prepare a standard stock solution by adding 15mg of nirmatrelvir to a 10 mL volumetric flask and adding 5 mL diluent, mixing for 2 minutes and making the volume to 10 mL with diluent (conc.of nirmatrelvir = 1500µg/mL).

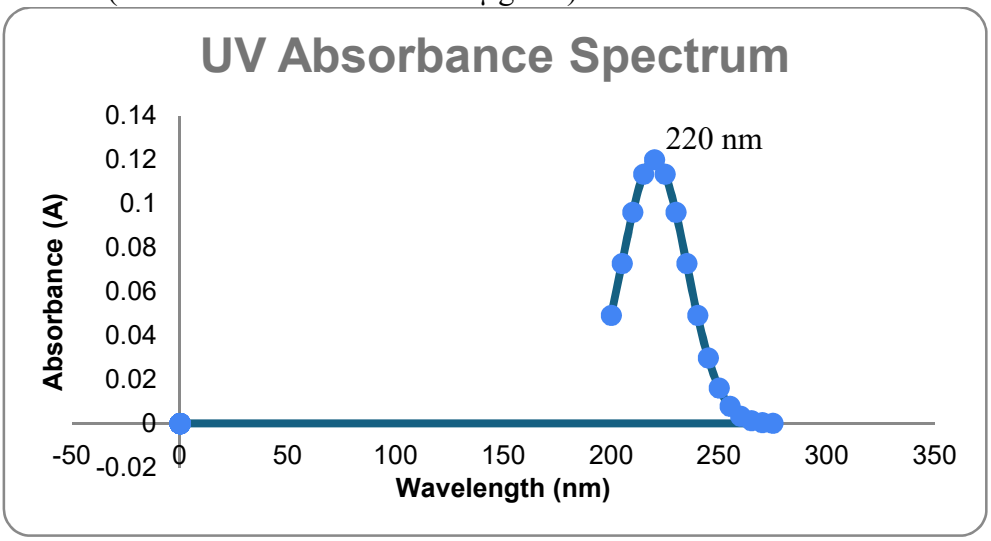


Figure 3: Lambda (λ) Max of Nirmatrelvir

Construction of Standard Graph for Nirmatrelvir

Calibration Curve of Standard Nirmatrelvir

Accurately weighed Nirmatrelvir which is equivalent to 100mg, then take a 100ml volumetric flask and add nirmatrelvir, dissolved in 25mL of ethanol. The volume was made up to 100ml by using phosphate buffer (pH 7.4) to obtain a primary stock solution – 1000µg/ml. From this primary stock solution 10ml was pipette out into a 100ml standard volumetric flask and make up to 100mL by using phosphate buffer (pH 7.4)[secondary stock solution]. From this secondary stock solution, aliquots of 2 ml, 4ml, 6ml, 8ml and 10ml were pipette out, and the volume is making up by using phosphate buffer (pH 7.4) to get drug concentration in the range of 2 - 12µg/ml. The absorbance of the resulting solution was then measured at 215nm using a UV spectrophotometer against phosphate buffer (pH 7.4) a blank. The standard curve was obtained by plotting concentration (µg/mL) value in X- axis and absorbance values in Y- axis.

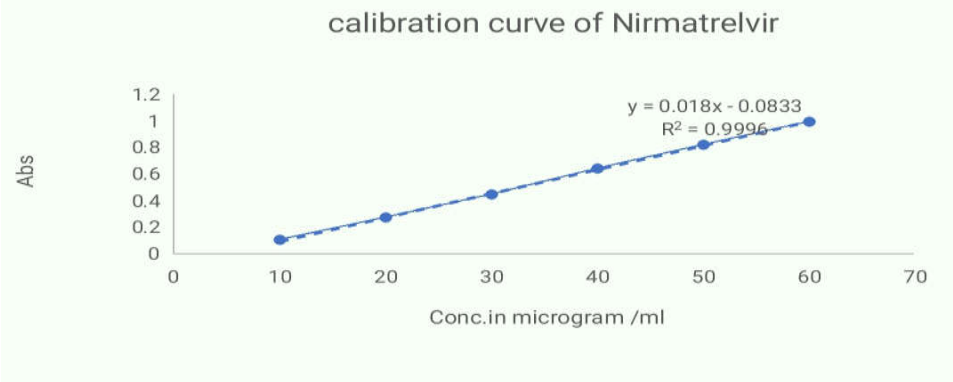


Figure 4: Calibration curve of Nirmatrelvir

B) Compatibility Studies

FTIR Spectroscopy

The FTIR study was used to determine how drugs and polymers interacted. This is to verify if the formulation composition was compatible, the drug, excipients, physical mixture and formulation peaks were measured.

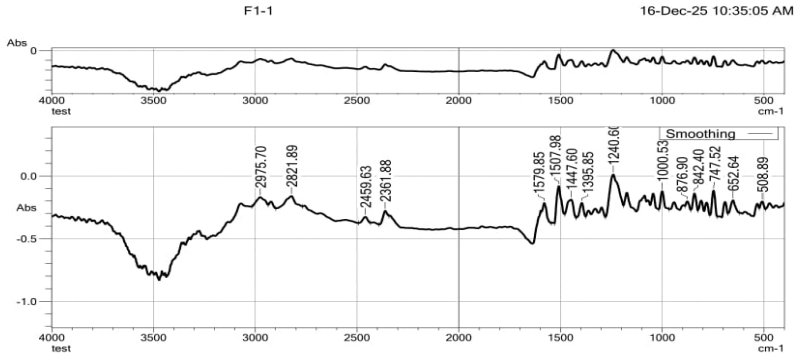


Figure 5: FT-IR Spectra of Nirmatrelvir

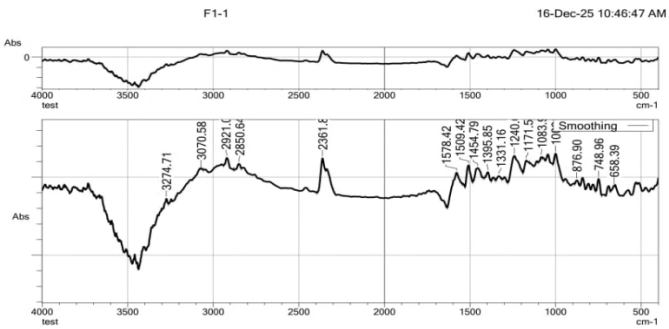


Figure 6: FT-IR Spectra of Physical Mixture

C) Post–Compression Studies [20, 21, 22]

General Appearance

This includes the tablet shape, size, colour (presence or absence), taste, odour, surface texture, physical defects, legibility of any identifying marks, and uniformity. (Table 5)

Size and Shape

The size and shape of a tablet are measurable physical attributes that can be monitored and controlled to ensure consistency. (Table 5)

Drug Content Uniformity

Tablets were randomly selected and powdered. A quantity of the powder equivalent to 50 mg of the model drug was dissolved in 100 ml of phosphate buffer (pH 7.4), stirred for 15 minutes, and filtered. Then, 1 ml of the filtrate was diluted to 100 ml with phosphate buffer (pH 7.4). The absorbance of this solution was measured at 250 nm using phosphate buffer (pH 7.4) as the blank, and the drug content was estimated. (Table 5)

Hardness Test

The force required to break the tablet across its diameter was recorded as its hardness. (Table 5)

Thickness

Each tablet was placed between the jaws of the calliper and the scale arm was gently slid to hold the tablet in place. The displayed reading was noted for each tablet. (Table 5)

Weight Variation

Tablets were randomly selected from each batch and weighed individually using a digital balance. The average tablet weight was calculated and compared to individual tablet weights. (Table 5)

Friability

Five tablets from each batch were accurately weighed and placed in a friabilator. The test was conducted at 25 rpm for 4 minutes. After completion, the tablets were reweighed, and friability was calculated. (Table 5)

Wetting Time (Wt)

A piece of tissue paper was folded twice and placed in a petri dish containing 6 ml of water. A tablet was placed on the paper, and the time required for complete wetting was measured using a stopwatch.

In Vitro Disintegration Study

Four tablets from each formulation were placed individually into four separate test tubes containing 600 mL of phosphate buffer (pH 6.8) in a disintegration apparatus. The apparatus was maintained at 37 + (or) - 0.5 ˚C and operated with gentle up-and-down movements. The time taken for complete tablet disintegration was recorded.

Table 4: Evaluation parameter of post-compression studies

Test Parameter	Batch F1
Size	Small
Shape	Round
Colour	White to off-white
Odour	Odourless
Surface Texture	Flat, Smooth And Slightly Chalky
Physical Flaws	No visible cracks or major breakage
Consistency	Uniform in size, shape, colour
Legibility	No imprint, score line, logo or identification mark
Drug content	98.67%

Hardness Test	3.3 ± 0.29 kg/cm^2
Thickness Test	3.4 ± 0.35 mm
Friability Test	0.7 ± 0.0%
Weight Variation	0.11%
SWetting Time	19.7 ± 1.53 sec
In Vitro Disintegration Study	30 sec

In Vitro Permeation Studies

In vitro permeation studies were carried out using a modified Franz diffusion cell with a regenerated cellulose dialysis membrane with a pore size of 2.5 nm. The membrane was stabilised and mounted between the donor and receptor compartments. The receptor compartment was filled with phosphate buffer (pH 7.4), maintained at 37 ± 0.2 °C and stirred continuously. The formulation was placed in the donor compartment. Samples were withdrawn at predetermined intervals, replacing with fresh medium was added. Drug permeation was quantified using a UV–Visible spectrophotometer at the appropriate wavelength.

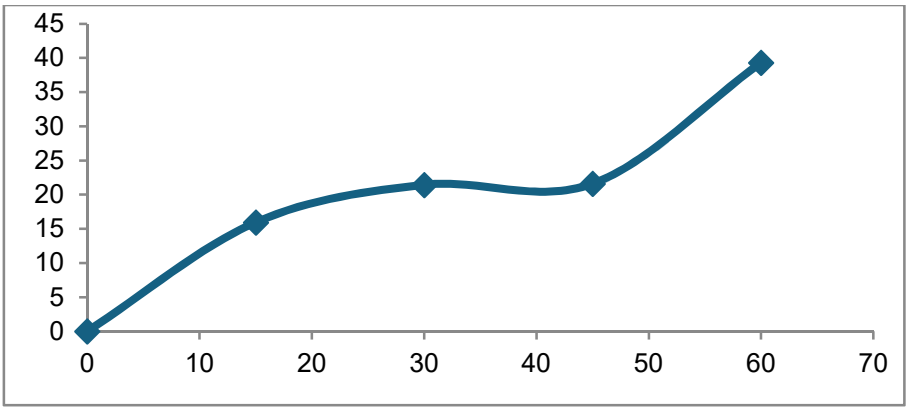


Figure 12: In vitro Permeation Profile of Nirmatrelvir sublingual tablet

15. CONCLUSION

The present study successfully demonstrated that Nirmatrelvir can be effectively formulated as a sublingual tablet using the direct compression technique. The formulated tablets exhibited satisfactory pre-compression and post-compression characteristics, rapid disintegration, acceptable mechanical strength, uniform drug content, and good patient-friendly properties. The sublingual route proved to be advantageous by providing rapid drug release, enhanced bioavailability and avoidance of first-pass metabolism, which is particularly beneficial in the treatment of acute viral infections such as COVID-19. FTIR studies confirmed formulation stability, and evaluation results indicated compliance with pharmacopoeial standards.

Overall, the developed Nirmatrelvir sublingual tablet formulation can be considered a promising and effective alternative to conventional oral dosage forms. Further research will be conducted during my higher studies to enhance and expand these findings.

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