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DESIGN AND DEVELOPMENT OF SUSTAINED RELEASE DOSAGE FORM FOR NIRMATRELVIR

*Akshat Gupta, [1]Sneha Singh, [2]Mohit Chaturvedi, [3]Akhilesh Gupta, [4]Amit Modi

*, 1, 2 3, 4College Of Pharmacy, Dr. A.P.J. Abdul Kalam University, Indore (M.P.)

ABSTRACT :

The COVID-19 pandemic necessitated the implementation of rapid treatment measures, and nirmatrelvir has emerged as a critical antiviral agent. Its effectiveness is significantly enhanced when administered in conjunction with Ritonavir due to improved systemic availability. However, the long-term use of Ritonavir is associated with serious side effects that necessitate alternative approaches. This article investigates the design and development of a sustained release (SR) dosage form of nirmatrelvir, aimed at eliminating the need for Ritonavir while maintaining therapeutic plasma levels over an extended duration. This strategy has the potential to reduce the frequency of dosing, improve patient compliance, and mitigate the adverse effects associated with supplementary medications such as Ritonavir.

Key Words: Pandemic, antiviral, conjunction, compliance

Introduction

When used in conjunction with Ritonavir as Paxlovid, Nirmatrelvir, a strong inhibitor of the SARS-CoV-2 major protease (Mpro), has shown remarkable success in treating COVID-19 by interfering with viral replication [1, 2]. By preventing CYP3A-mediated metabolism, Ritonavir acts as a pharmacokinetic enhancer, raising the plasma concentrations of Nirmatrelvir [3]. Ritonavir's long-term usefulness is, however, limited by its substantial risk of hepatotoxicity and drug-drug interactions [4].

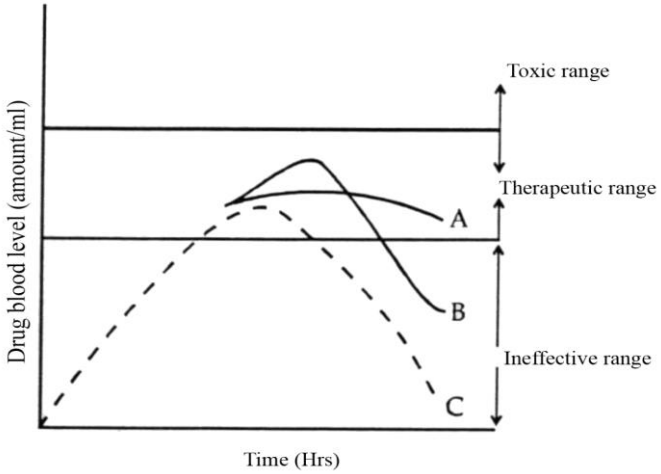

Figure 1: Relationship between the controlled release (A) prolonged release (B) and conventional release (C) systems

In order to prolong therapeutic levels and reduce variations in plasma drug concentrations, sustained release formulations are made to release a medication at a predefined pace [5]. By reducing or doing away with the requirement for Ritonavir, such formulations may be able to maintain Nirmatrelvir's antiviral activity and allay safety worries

Materials and Methods

Drug Profile and Preformulation Studies

Nirmatrelvir belongs to BCS Class III since it is a hydrophilic molecule with low permeability and high water solubility [6]. Solubility analysis, pKa

calculation, FTIR and DSC compatibility testing with excipients, and stability evaluation under ICH-recommended settings were all part of the preformulation investigations. Excipient selection and formulation improvement were guided by the findings.

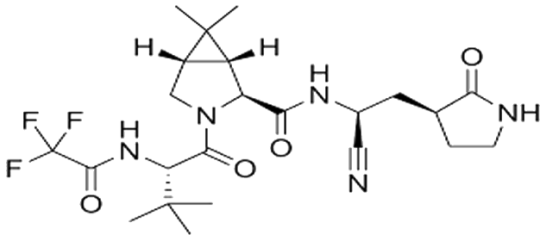

Figure 2: Molecular Structure of Nirmatrelvir

Selection of Polymers and Excipients

To adjust the drug release profile, hydrophilic matrix-forming polymers such sodium alginate and hydroxypropyl methylcellulose (HPMC K15M and K100M) were used [7]. Because of its high compressibility, microcrystalline cellulose (MCC) was used as a diluent, while talc and magnesium stearate were used as glidants and lubricants, respectively [8].

Formulation Technique

Direct compression, an economical and scalable technique appropriate for medications that are sensitive to moisture, such as nimtrelvir, was used to make the tablets. To assess their effects on release kinetics and physical characteristics, many batches with various polymer concentrations were made.

Evaluation of Formulated Tablets

Physical Characteristics: According to USP guidelines, every tablet batch was tested for weight fluctuation, thickness, hardness, friability, and drug content. The optimized batch had a drug content of 98–102%, homogeneous weight, hardness over 5 kg/cm2, and friability below 0.8%. [9].

Parameter	Observed Results	Key Points	Significance in SR Formulation
Hardness	Average: **8.5 kg/cm²** Minimal variation	- Ensures mechanical strength- Maintains integrity during handling- Supports controlled drug release	Prevents premature breakage or rapid release; enables consistent prolonged therapeutic effect
Friability	**< 1%** (within acceptable limits)	- Indicates resistance to chipping/cracking- Enhances appearance and durability- Ensures consistent performance	Confirms robustness during packaging/transport; critical for preserving release profile
Physical Appearance	Uniform shape, color, and smooth finish, No visible defects	- Reflects good manufacturing quality- Enhances patient trust- Reduces environmental and microbial vulnerability	Promotes patient compliance; supports uniform dissolution and stability

In Vitro Drug Release Studies: Using USP Type II dissolving equipment, release tests were conducted at 37°C in phosphate buffer with a pH of 6.8. Over a 12-hour period, batches with greater HPMC concentrations had a regulated release pattern. Zero-order, first-order, Higuchi, and Korsmeyer-Peppas models were used to assess drug release kinetics. Zero-order release was observed in the optimized batch ($R2 = 0.991$), suggesting a steady release rate that is unaffected by concentration [10].

Compatibility and Stability: The medication and excipients did not interact chemically, according to FTIR and DSC analyses. Stability was confirmed by three months of accelerated stability testing at 40°C/75% RH in accordance with ICH recommendations, which showed no appreciable changes in the drug's physical composition, release profile, or physical appearance [11].

Results and Discussion

Nirmatrelvir's release was effectively extended for up to 12 hours by the sustained release matrix tablet. The polymer ratio was carefully adjusted to strike a compromise between mechanical integrity and medication release rate. Compared to HPMC K15M, HPMC K100M showed superior matrix integrity; nevertheless, a combination of the two allowed synergistic control over drug release [12]. A combination of diffusion and erosion processes is implied by the anomalous (non-Fickian) transport suggested by the Korsmeyer-Peppas exponent ($n \approx 0.67$), [13]. This formulation may be able to sustain therapeutic levels of Nirmatrelvir from a pharmacokinetic perspective without the need for Ritonavir to block metabolism. This might lessen the negative interactions and hepatic burden related to coadministration of Ritonavir [14].

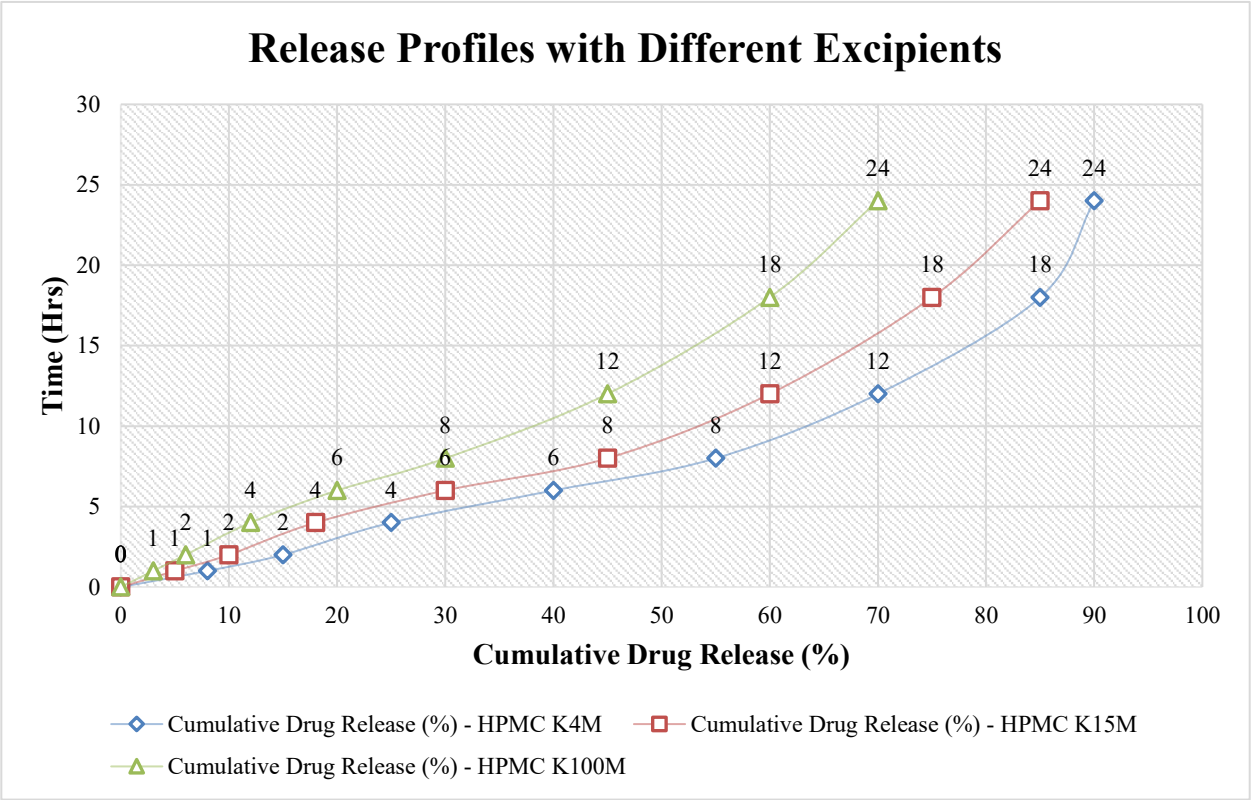

Figure 3: Release Profiles with Different Excipients

Conclusion

In vitro, the sustained release formulation of Nirmatrelvir created in this study showed encouraging outcomes in terms of stability, mechanical resilience, and prolonged drug release. In order to improve patient safety and adherence, this formulation may open the door for independent Nirmatrelvir treatment by attaining a zero-order release profile and appropriate pharmaceutical features. In order to confirm the pharmacokinetic advantages seen in vitro, next approaches will involve clinical correlation and in vivo bioavailability investigations.

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