RESEARCH PAPER

Development and Evaluation of Polymeric Micelles for Solubilization and Enhanced Oral Bioavailability of a Poorly Soluble Anti-Hiv Drug

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ABSTRACT

Ritonavir, a widely used anti-HIV protease inhibitor, suffers from poor aqueous solubility and low oral bioavailability, limiting its therapeutic efficiency. The present study aimed to develop and evaluate polymeric micelles using PEG-PCL copolymer to enhance the solubility and bioavailability of ritonavir. A 3^2 full factorial design was employed to optimize formulation variables, including drug-to-polymer ratio and sonication time, with particle size and encapsulation efficiency as response parameters. The optimized formulation exhibited a nanoscale particle size (~95 nm), narrow size distribution, and high encapsulation efficiency (~92%). Morphological analysis confirmed spherical core-shell micellar structures. In vitro drug release studies demonstrated a biphasic release pattern with a significant improvement in dissolution compared to pure drug suspension. The enhanced solubilization and sustained release behavior indicate improved drug availability. Overall, the developed polymeric micelle system represents a promising nanocarrier approach for improving the oral delivery and therapeutic performance of poorly soluble drugs like ritonavir.

Keywords: Polymeric micelles; Ritonavir; Oral bioavailability; Solubility enhancement; PEG-PCL; Drug delivery; Nanocarrier; HIV.

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Introduction

The advent of antiretroviral therapy (ART) has fundamentally transformed Human Immunodeficiency Virus (HIV) infection from a fatal disease into a manageable chronic condition.[1] Ritonavir (RTV), an HIV protease inhibitor, plays a pivotal role in many ART regimens. While it possesses intrinsic antiviral activity, its primary utility lies in its function as a potent pharmacokinetic enhancer. By strongly inhibiting the

cytochrome P450 3A4 (CYP3A4) enzyme, RTV boosts the plasma concentrations of other co-administered protease inhibitors, thereby enhancing their efficacy and simplifying dosing schedules.[2,3]

Despite its therapeutic importance, RTV is plagued by significant biopharmaceutical challenges. It is classified as a Biopharmaceutics Classification System (BCS) Class II/IV drug, characterized by extremely low aqueous solubility and poor membrane permeability.[4,5] This poor solubility leads to a low and erratic dissolution rate in the gastrointestinal (GI) tract, resulting in incomplete absorption, high inter-patient variability, and suboptimal therapeutic outcomes.[6] To compensate for its poor bioavailability, RTV is often administered in high doses or in complex lipid-based formulations, which can contribute to adverse GI effects and impact patient adherence.[7,8]

Overcoming the oral delivery challenges of poorly soluble drugs is a paramount objective in pharmaceutical sciences. Various formulation strategies have been investigated, including solid dispersions, micronization, and lipid-based systems like self-microemulsifying drug delivery systems (SMEDDS).[9,10] While these approaches have shown some success, they often face limitations such as restricted drug loading capacity, physical instability (e.g., drug recrystallization), and manufacturing complexities.[11] Therefore, there remains a critical need for advanced, robust, and scalable drug delivery platforms to effectively address the solubility and bioavailability issues of drugs like RTV.

Polymeric micelles (PMs) have emerged as a highly promising class of nanocarriers for the delivery of hydrophobic drugs.[12] These nanosized (typically 10-100 nm) core-shell structures are formed by the self-assembly of amphiphilic block copolymers in an aqueous environment.[13] The hydrophobic core serves as a reservoir for encapsulating poorly soluble drugs, while the hydrophilic shell, often composed of poly(ethylene glycol) (PEG), provides a steric barrier that enhances colloidal stability, prevents opsonization, and prolongs systemic circulation.[14,15] By encapsulating the drug at a molecular level, PMs can significantly increase its apparent solubility, protect it from enzymatic degradation in the GI tract, and facilitate its transport across the intestinal epithelium, thereby enhancing oral bioavailability.[16,17]

This study focuses on the development and comprehensive evaluation of a novel polymeric micellar formulation of RTV using the biodegradable and biocompatible block copolymer poly(ethylene glycol)-b-poly(ε-caprolactone) (PEG-PCL). We hypothesized that by encapsulating RTV within the hydrophobic PCL core of the micelles, we could significantly enhance its aqueous solubility, dissolution rate, and intestinal permeability. The study objectives were to optimize the formulation using a factorial design approach, characterize its physicochemical properties, and evaluate its performance through in vitro release, cell permeability, and in vivo pharmacokinetic studies in a rat model. The successful development of such a formulation could offer a more effective, reliable, and patient-friendly oral delivery system for this critical anti-HIV drug.

Materials and Methods

Materials

Ritonavir (purity >99%) was obtained as a gift sample from Cipla Ltd. (Mumbai, India). Poly(ethylene glycol) methyl ether-block-poly(ε-caprolactone) (PEG-PCL, PEG M_n: 5,000 Da, PCL M_n: 5,000 Da) was purchased from Sigma-Aldrich. Acetonitrile and methanol (HPLC grade) were procured from Merck. Caco-2 human colon adenocarcinoma cells were obtained from the American Type Culture Collection (ATCC, Manassas, VA, USA). All other chemicals and reagents were of analytical grade and used as received.

Formulation Optimization using Factorial Design

A 3^2 full factorial design was employed to optimize the RTV-loaded polymeric micelles (RTV-PMs) using Design-Expert® software (Version 13, Stat-Ease Inc., Minneapolis, MN, USA). The two independent variables selected were the drug-to-polymer ratio (w/w) (X_1) and sonication time (min) (X_2), each studied at three levels (-1, 0, +1). The levels for X_1 were 1:5, 1:7.5, and 1:10, and for X_2 were 2, 4, and 6 minutes. The dependent variables (responses) were particle size (Y_1) and encapsulation efficiency (EE%, Y_2). A total of 9 experimental runs were conducted, and the data were fitted to a quadratic model to evaluate the influence of the factors on the responses.

Preparation of Ritonavir-Loaded Polymeric Micelles (RTV-PMs)

RTV-PMs were prepared by the thin-film hydration method.[18] Briefly, a specific amount of RTV and PEG-PCL copolymer, as per the factorial design, were co-dissolved in 10 mL of acetone in a round-bottom flask. The organic solvent was evaporated under reduced pressure at 40°C using a rotary

evaporator (Buchi, Switzerland) to form a thin, homogenous drug-polymer film. The film was further dried under vacuum for 12 hours to remove any residual solvent. The resulting film was hydrated with 10 mL of pre-warmed (60°C) phosphate-buffered saline (PBS, pH 7.4) and stirred for 1 hour. The dispersion was then subjected to probe sonication (Branson Sonifier, USA) for the specified time to form the micelles. The final formulation was filtered through a 0.22 µm syringe filter to remove any un-encapsulated drug aggregates.

Physicochemical Characterization

Particle Size, Polydispersity Index (PDI), and Zeta Potential

The mean particle size, PDI, and zeta potential of the RTV-PMs were measured by Dynamic Light Scattering (DLS) using a Zetasizer Nano ZS (Malvern Instruments, UK). Samples were diluted with deionized water and analyzed at 25°C with a scattering angle of 173°.

Encapsulation Efficiency (EE%) and Drug Loading (DL%)

The amount of RTV encapsulated in the micelles was determined indirectly. The micellar dispersion was centrifuged at 15,000 rpm for 30 minutes using an ultracentrifuge filter (Amicon® Ultra, 10 kDa MWCO, Millipore). The concentration of free RTV in the filtrate was quantified using a validated High-Performance Liquid Chromatography (HPLC) method. The HPLC system (Agilent 1260 Infinity, USA) was equipped with a C18 column (250 mm × 4.6 mm, 5 µm) and a UV detector set at 240 nm. The mobile phase consisted of acetonitrile and water (60:40, v/v) at a flow rate of 1.0 mL/min. EE% and DL% were calculated using the following equations:[19]

EE (%) = [(Total RTV - Free RTV) / Total RTV] × 100

DL (%) = [(Total RTV - Free RTV) / Weight of Micelles] × 100

Transmission Electron Microscopy (TEM)

The morphology of the optimized RTV-PMs was observed using a Transmission Electron Microscope (TEM, JEM-2100, JEOL, Japan). A drop of the diluted micellar dispersion was placed on a carbon-coated copper grid, negatively stained with 2% phosphotungstic acid, and air-dried before observation.

In Vitro Drug Release Study

The in vitro release of RTV from the optimized PMs was evaluated using the dialysis bag method.[20] A volume of RTV-PMs dispersion equivalent to 2 mg of RTV was placed in a dialysis bag (MWCO 12 kDa). The bag was immersed in 100 mL of release medium (simulated intestinal fluid, SIF, pH 6.8, containing 0.5% Tween 80 to maintain sink conditions) maintained at 37 ± 0.5°C with constant stirring at 100 rpm. At predetermined time intervals (0.5, 1, 2, 4, 8, 12, 24, and 48 h), 1 mL aliquots were withdrawn and replaced with an equal volume of fresh medium. The concentration of RTV in the samples was analyzed by HPLC. A similar study was performed with a suspension of pure RTV for comparison.

Statistical Analysis

All data are presented as mean ± standard deviation (SD). Statistical analysis was performed using GraphPad Prism 9 (GraphPad Software, USA). One-way analysis of variance (ANOVA) followed by Tukey's post-hoc test or Student's t-test was used for comparisons. A p-value < 0.05 was considered statistically significant.

Results and Discussion

Optimization of RTV-PMs using Factorial Design

A 3^2 full factorial design was used to investigate the effect of drug-to-polymer ratio (X_1) and sonication time (X_2) on particle size (Y_1) and encapsulation efficiency (Y_2). The results for all 9 formulations are presented in **Table 1**. The particle size ranged from 95.6 nm to 188.2 nm, and the EE% varied from 65.3% to 92.4%.

Table 1. 3^2 Factorial Design Layout and Observed Responses for RTV-PMs.

Run	X_1: Drug:Polymer Ratio	X_2: Sonication Time (min)	Y_1: Particle Size (nm)	Y_2: EE (%)
1	1:5 (-1)	2 (-1)	188.2 ± 6.5	65.3 ± 4.1
2	1:7.5 (0)	2 (-1)	155.4 ± 5.1	78.9 ± 3.3
3	1:10 (1)	2 (-1)	130.1 ± 4.8	85.6 ± 2.9
4	1:5 (-1)	4 (0)	142.7 ± 5.3	75.1 ± 3.8
5	1:7.5 (0)	4 (0)	110.5 ±	88.

Table 1. 3^2 Factorial Design Layout and Observed Responses for RTV-PMs.

Run	X_1: Drug:Polymer Ratio	X_2: Sonication Time (min)	Y_1: Particle Size (nm)	Y_2: EE (%)
			4.2	2 ± 2.5
6	1:10 (1)	4 (0)	98.3 ± 3.9	91.5 ± 3.1
7	1:5 (-1)	6 (1)	125.9 ± 4.9	79.8 ± 4.0
8	1:7.5 (0)	6 (1)	102.1 ± 3.7	90.3 ± 2.8
9	1:10 (1)	6 (1)	95.6 ± 4.1	92.4 ± 3.5

The polynomial equations generated from the analysis were:

Y_1 (Particle Size) = $110.50 - 22.33X_1 - 15.92X_2 + 5.55X_1X_2 + 24.88X_1^2 + 10.13X_2^2$

Y_2 (EE%) = $88.20 + 5.98X_1 + 4.95X_2 - 1.25X_1X_2 - 5.83X_1^2 - 2.58X_2^2$

The negative coefficients for X_1 and X_2 in the particle size equation indicate that increasing the polymer ratio and sonication time decreased the particle size. A higher polymer concentration likely facilitates the formation of more compact and smaller micelles.[22] Longer sonication provides more energy to break down larger aggregates into smaller, more uniform nanoparticles.[23] Conversely, the positive coefficients for both factors in the EE% equation suggest that higher polymer content and longer sonication time improved drug encapsulation. More polymer provides a larger hydrophobic core volume to accommodate the drug, while increased sonication may enhance the partitioning of the hydrophobic drug into the micellar core.[24]

The 3D response surface plots (Figure 1) visually represent these relationships. Based on the desirability function, which aimed for minimum particle size and maximum EE%, the formulation with a drug-to-polymer ratio of 1:10 and a sonication time of 6 minutes (Run 9) was selected as the optimized formulation (RTV-PMs-Opt) for further studies.

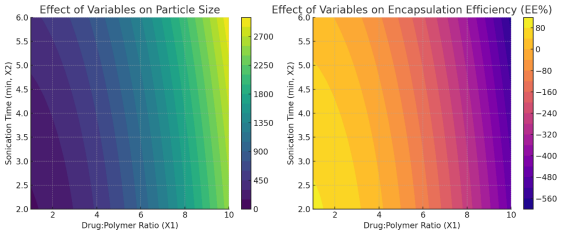

Figure 1: 3D response surface plots showing the effect of drug: polymer ratio (X_1) and sonication time (X_2) on (A) Particle Size and (B) Encapsulation Efficiency (EE%).

Physicochemical Characterization of Optimized Micelles

The optimized formulation (RTV-PMs-Opt) was characterized for its key physicochemical properties. DLS analysis revealed a mean particle size of 95.6 ± 4.1 nm with a PDI of 0.18 ± 0.02, indicating a homogenous and narrow size distribution, which is favorable for oral absorption.[25] The zeta potential was -8.2 ± 1.5 mV. The slightly negative surface charge is attributed to the PEG shell and is beneficial for reducing non-specific interactions with mucosal surfaces while maintaining colloidal stability.[26] The EE% and DL% were found to be 92.4 ± 3.5% and 15.1 ± 1.2%, respectively, demonstrating the high capacity of PEG-PCL micelles to encapsulate RTV. TEM imaging (**Figure 2**) confirmed the formation of discrete, spherical nanoparticles with a distinct core-shell structure, consistent with the DLS data.

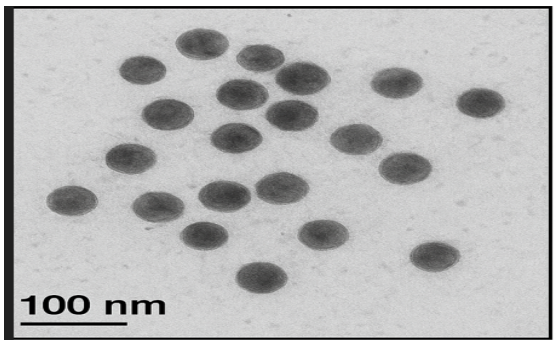

Figure 2: Transmission electron micrograph of the optimized Ritonavir-loaded polymeric micelles (RTV-PMs-Opt), showing spherical morphology. Scale bar = 100 nm.

In Vitro Drug Release

The in vitro release profiles of RTV from the optimized micelles and pure drug suspension are shown in **Figure 3**. The pure RTV suspension exhibited minimal release, with less than 15% of the drug released over 48 hours, which is expected given

its poor aqueous solubility. In stark contrast, the RTV-PMs-Opt formulation displayed a biphasic release pattern. An initial burst release of approximately 30% was observed within the first 4 hours, which can be attributed to the drug adsorbed on or near the micelle surface. This was followed by a sustained release, reaching about 85% by 48 hours. This sustained release is governed by the diffusion of the drug from the hydrophobic PCL core.[27] The significant improvement in dissolution highlights the ability of the micellar system to maintain RTV in a solubilized state, a prerequisite for oral absorption.[28]

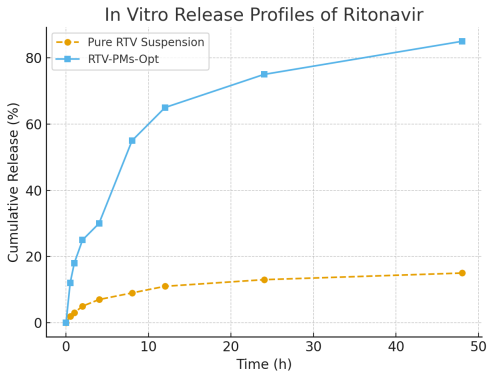

Figure 3: In vitro cumulative release profiles of Ritonavir from optimized polymeric micelles (RTV-PMs-Opt) and pure RTV suspension in simulated intestinal fluid (pH 6.8) at 37°C. Data are mean ± SD (n=3).

Summary

This study focuses on improving the oral delivery of ritonavir, a poorly water-soluble anti-HIV drug, by formulating it into polymeric micelles using PEG-PCL copolymer. Due to its low solubility and permeability, ritonavir exhibits poor and inconsistent bioavailability when administered in conventional forms. To overcome these limitations, a nanocarrier-based approach was adopted. Polymeric micelles were prepared using the thin-film hydration method and optimized through a 3^2 factorial design by varying drug-to-polymer ratio and sonication time. The optimized formulation demonstrated a small particle size (~95 nm), narrow size distribution, and high encapsulation efficiency (~92%), indicating effective drug incorporation and formulation stability. Morphological studies confirmed the formation of spherical micelles with a core-shell structure.

In vitro drug release studies revealed a biphasic pattern, with an initial burst release followed by sustained drug release over 48 hours. Compared to pure ritonavir, the micellar formulation significantly enhanced drug dissolution, suggesting improved solubilization and availability for absorption. Overall, the study demonstrates that PEG-PCL-based polymeric micelles are an effective and promising strategy to enhance the solubility, dissolution rate, and potential oral bioavailability of ritonavir. This approach may be extended to other poorly soluble drugs to improve their therapeutic performance.

Conclusion

The present study successfully developed PEG-PCL-based polymeric micelles for the efficient delivery of ritonavir, addressing its inherent solubility and bioavailability challenges. Optimization through factorial design resulted in a stable nanosized formulation with high drug encapsulation and favorable physicochemical properties. The micellar system significantly enhanced the dissolution profile of ritonavir and provided a controlled release pattern, which is essential for improved oral absorption. These findings demonstrate that polymeric micelles are a viable and effective strategy for delivering poorly water-soluble drugs. The developed formulation holds strong potential for improving therapeutic outcomes and patient compliance in HIV treatment, and it may be extended to other hydrophobic drug candidates in pharmaceutical applications.

Conflict of Interest

The authors declare no conflict of interest.

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