Lipid-Polymer Hybrid Nanocarriers to Overcome Intestinal Permeability Barriers in Oral Delivery of Risedronate for Osteoporosis Therapy: Preformulation and Analytical Studies

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Abstract: Osteoporosis remains a major global health concern, and risedronate sodium is a first-line bisphosphonate for its treatment. However, its oral bioavailability is limited to approximately 0.65% due to poor intestinal permeability despite high aqueous solubility (BCS Class III). The present study aimed to develop and optimize risedronate sodium-loaded lipid-polymer hybrid nanoparticles using a double-emulsion solvent evaporation technique to enhance intestinal permeation. A systematic approach involving preformulation studies, analytical method and formulation development was employed. Drug authentication was performed using physical characterization, Fourier-transform infrared spectroscopy, differential scanning calorimetry, melting point determination, and equilibrium solubility studies. A UV-visible spectrophotometric method was developed and validated at 262 nm in distilled water, 0.1 N HCl, and phosphate buffer pH 6.8. The drug exhibited a melting point of 262.86°C with characteristic FTIR peaks confirming structural integrity. Calibration curves showed excellent linearity over the concentration range of 10–50 µg/mL, while solubility studies confirmed high aqueous solubility (62.7 ± 0.05 mg/mL in distilled water) and negligible solubility in organic solvents, supporting the selection of the $W_1/O/W_2$ double-emulsion solvent evaporation technique for LPHN preparation. These findings provide a robust foundation for formulation optimization and the subsequent development of LPHNs to improve intestinal permeability of risedronate sodium.

Keywords: Risedronate sodium; Lipid- polymer hybrid nanoparticles; Osteoporosis; Preformulation studies; Intestinal Permeability.

Introduction

Osteoporosis is a chronic metabolic bone condition characterized by low bone mineral density and degeneration of bone microarchitecture, which increases bone fragility and fracture risk. It is one of the most common skeletal illnesses globally, particularly among postmenopausal women and the elderly. Osteoporotic fractures, particularly those affecting the hip, vertebrae, and wrist, have a major impact on morbidity, mortality, and healthcare costs. Bisphosphonates, pyrophosphate analogues that bind tightly to hydroxyapatite crystals in bone and inhibit osteoclast-mediated bone resorption, remain the most widely used therapeutic class for osteoporosis, with nitrogen-containing agents such as alendronate, risedronate, ibandronate and zoledronic acid demonstrating significant clinical success [1, 2]. Risedronate sodium is among the most widely prescribed bisphosphonates owing to its potent antiresorptive activity and favourable safety profile; however, it exhibits extremely low oral bioavailability (approximately 0.6-0.7%) because of its high polarity, limited intestinal permeability and propensity to chelate dietary divalent cations [3-5]. Conventional formulation strategies, such as enteric-coated tablets and gastro-retentive systems, have not sufficiently overcome this permeability barrier. Lipid-polymer hybrid nanoparticles (LPHNs), which combine the encapsulation stability of a polymeric core with the membrane-interactive properties of a lipid shell, have emerged as a promising nanocarrier platform for enhancing the oral absorption of poorly permeable drugs [6], as reviewed in our earlier work presented at Conference 1.

Related Work

Several strategies have been explored to improve the oral delivery of risedronate and other poorly permeable bisphosphonates, as summarized in our earlier comparative review (Conference 1) and condensed in Table 1.

Table 1. Condensed comparison of prior delivery strategies for risedronate with the proposed LPHN-based approach

Delivery Strategy	Risedronate Permeability Addressed	Nanocarrier-Based Delivery	Oral LPHN Strategy	Ref
Conventional oral / sublingual formulations (tablets, spray)	Yes	No	No	[2,3]
Polymeric nanoparticles / liposomes (chitosan nanoparticles, mucoadhesive liposomes)	Yes	Yes	No	[8,9]
Gastroretentive xyloglucan raft system	Yes	No	No	[7]
Lipid-polymer hybrid nanoparticles (generic systems)	No	Yes	Yes	[5,6]
This work - Risedronate sodium-loaded LPHNs (preformulation & analytical groundwork)	Yes	Yes	Yes	This work

Key Contributions: This study presents the initial experimental work on the development of risedronate sodium-loaded lipid–polymer hybrid nanoparticles for improving oral drug delivery in osteoporosis. The developed UV-visible spectrophotometric method provides a reliable approach for quantitative estimation of the drug during formulation and evaluation. The solubility profile of risedronate sodium supports the selection of the $W_1/O/W_2$ double-emulsion solvent evaporation technique for nanoparticle preparation. This work represents an important step toward the development of a lipid–polymer hybrid nanocarrier system designed to improve the oral bioavailability of risedronate sodium for osteoporosis therapy.

Method, Experiments and Results

Aim and Objectives

Aim: To develop and optimize risedronate sodium-loaded lipid-polymer hybrid nanoparticles using a double emulsion solvent evaporation technique to overcome intestinal permeability barriers.

Objectives:

1. To carry out the pre-formulation studies of risedronate sodium.
2. To perform preliminary screening of the excipients and the process for preparation of risedronate-loaded LPHNs.
3. To carry out analytical method development of risedronate sodium by UV spectroscopy.
4. To formulate and develop risedronate-loaded LPHNs.
5. To carry out evaluation and characterization of risedronate-loaded LPHNs.
6. To carry out stability studies of risedronate-loaded LPHNs (ICH Q1A(R2) Guidelines).

Analytical Method Development (UV Spectroscopy)

UV-spectrophotometric calibration curves for risedronate sodium were developed in three media distilled water, 0.1N HCl (simulating gastric fluid) and phosphate buffer pH 6.8 (simulating intestinal fluid) to support subsequent in vitro release studies. For each medium, 50 mg of RS was accurately weighed, dissolved and made up to 50 mL to obtain Stock Solution I (1 mg/mL). Ten millilitres of Stock Solution I was diluted to 100 mL with the respective medium to obtain Stock Solution II (100 µg/mL). Aliquots of 1, 2, 3, 4 and 5 mL of Stock Solution II were transferred to separate 10 mL volumetric flasks and made up to

volume with the respective medium to prepare 10, 20, 30, 40 and 50 µg/mL working solutions. Absorbance was measured at 262 nm in triplicate; the mean ± SD was calculated, and the absorbance-concentration data were fitted by linear regression.

Table 2. Calibration data for RS (λ = 262 nm, n = 3)

Concentration (µg/mL)	Mean ± SD (Distilled Water)	Mean ± SD (0.1N HCl)	Mean ± SD (PBS 6.8)
10	0.120 ± 0.001	0.119 ± 0.002	0.178 ± 0.001
20	0.270 ± 0.003	0.234 ± 0.002	0.320 ± 0.001
30	0.390 ± 0.002	0.345 ± 0.002	0.472 ± 0.002
40	0.510 ± 0.001	0.431 ± 0.002	0.599 ± 0.001
50	0.690 ± 0.002	0.556 ± 0.003	0.700 ± 0.002

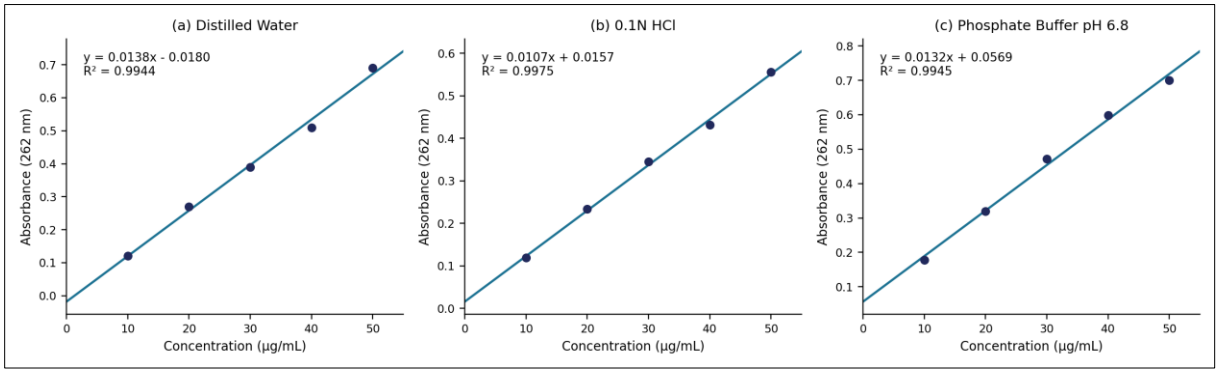


Figure 1. UV-spectrophotometric calibration curves of risedronate sodium at 262 nm in (a) distilled water (b) 0.1N HCl and (c) phosphate buffer pH 6.8.

Preformulation Studies

Drug Authentication

Risedronate sodium was examined for physical appearance, which was confirmed as a white to off-white, free-flowing powder. Melting point was determined by Thiele method (261-264 °C) and by differential scanning calorimetry (262.86 °C).

FTIR Spectral Analysis

The FTIR spectrum of risedronate sodium (Figure 2) was recorded



Figure 2. FTIR spectrum of risedronate sodium.

Solubility Determination

An excess amount of RS was added to 5 mL of each solvent- distilled water, deionized water, 0.1N HCl, phosphate buffer pH 6.8, methanol, ethanol, acetone and ethyl acetate in separate glass tubes to ensure saturation. The tubes were placed in an isothermal shaker bath maintained at 37 ± 0.5 °C and agitated at 100 rpm for 24 h to reach equilibrium. Suspensions were then centrifuged at 10,000 rpm for 30 min, and the clear supernatant was suitably diluted and analyzed by UV-visible spectrophotometry.

Table 3. Solubility of risedronate sodium in various solvents (mean ± SD, n = 3)

Solvent / Medium	Solubility (mg/mL)	Inference
Distilled Water	62.7 ± 0.05	Freely soluble
Deionized Water	62.2 ± 0.09	Freely soluble
0.1N HCl (pH 1.2)	53.3 ± 0.04	Soluble
Phosphate Buffer pH 6.8	59.9 ± 0.03	Freely soluble
Methanol	0.35 ± 0.03	Very slightly soluble
Ethanol	0.15 ± 0.02	Very slightly soluble
Acetone	0.02 ± 0.003	Practically insoluble
Ethyl Acetate	0.01 ± 0.002	Practically insoluble

Preparation of Risedronate Sodium-Loaded Lipid Polymer Hybrid Nanoparticles (LPHNs) by Double Emulsion Solvent Evaporation Method [10]

The LPHNs containing risedronate sodium were prepared using a modified double emulsion ($W_1/O/W_2$) solvent evaporation technique. Initially, 50 mg of risedronate sodium was accurately weighed and dissolved in 2 mL of deionized water under magnetic stirring at 500 rpm for 10 min to obtain a clear and homogeneous internal aqueous phase (W_1). Separately, the organic phase (O) was prepared by dissolving 300 mg of Eudragit RS100 and 150 mg of ethyl cellulose in 15 mL of an ethanol: ethyl acetate (7:3, v/v) solvent mixture, followed by the addition of 200 mg of stearic acid and 0.50 mL of oleic acid. The mixture was stirred at 45–50°C until a clear and homogeneous solution was obtained. The internal aqueous phase was then added dropwise into the organic phase under continuous stirring, and the resulting primary water-in-oil (W_1/O) emulsion was immediately subjected to probe sonication at 40% amplitude for 2 min in an ice bath to minimize heat generation. Subsequently, the external aqueous phase (W_2) was prepared by dissolving sodium lauryl sulfate (0.5% w/v) in 100 mL of deionized water with continuous magnetic stirring. The primary emulsion was slowly introduced into the external aqueous phase under stirring and homogenized at 12,000–15,000 rpm for 10 min to produce a stable $W_1/O/W_2$ double emulsion. To further reduce the droplet size and obtain nanosized particles, the emulsion was probe-sonicated at 40% amplitude in pulse mode (5 s on/off) for 5 min while maintaining the sample in an ice bath. The resulting nanoemulsion was stirred continuously at 500 rpm at room temperature for 4–6 h to facilitate complete evaporation of ethanol and ethyl acetate, leading to precipitation of the polymers and solidification of the lipid phase, thereby forming lipid–polymer hybrid nanoparticles. During this process, stearic acid and oleic acid constituted the lipid matrix, whereas Eudragit RS100 and ethyl cellulose formed the surrounding polymeric framework, entrapping risedronate sodium within the nanoparticle core while sodium lauryl sulfate stabilized the particle surface. Finally, the nanoparticle suspension was purified by centrifugation at 15,000 rpm for 30 min at 4°C, after which the supernatant was discarded, and the nanoparticle pellet was washed three times with deionized water before further characterization.

Discussion

Developing oral nanocarriers for BCS Class III drugs requires balancing entrapment stability with enhanced intestinal permeability. The analytical procedures developed here were linear ($R^2 > 0.99$) across gastric

and intestinal fluids. Thermal and spectroscopic data confirmed the identity and structural integrity of risedronate sodium. Saturation solubility testing verified that risedronate sodium remains practically insoluble in organic solvents while being freely soluble in aqueous environments (>50 mg/mL). This confirms that its primary limitation is intestinal permeability rather than dissolution. The high aqueous solubility also dictates the choice of a double emulsion (W1/O/W2) approach. In this framework, the lipid-polymer shell protects the entrapped hydrophilic drug core from premature degradation and prevents luminal divalent cation chelation.

Conclusion

1. **Problem Statement Addressed / Motivation:** This study addressed the poor oral bioavailability of risedronate sodium by establishing the analytical and preformulation basis for developing LPHNs.
2. **Method Used / Proposed Strategy: P**hysicochemical profiling, UV spectrophotometric method validation, and preformulation studies (FTIR, DSC, melting point, and solubility) were performed to support the development of LPHNs using the $W_1/O/W_2$ double emulsion solvent evaporation technique.
3. **Key Findings:** The analytical methods demonstrated excellent linearity ($R^2 > 0.99$), while preformulation studies confirmed the drug's identity, purity, and BCS Class III nature, supporting the suitability of the proposed formulation approach.
4. **Limitations and Future Work:** The present work is limited to analytical and preformulation studies. Future research will focus on LPHN formulation optimization, physicochemical and structural characterization, in vitro and ex vivo evaluation, and stability studies according to ICH guidelines.

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