Lipid-Polymer Hybrid Nanocarriers to Overcome Intestinal Permeability Barriers in Oral Delivery of Risedronate for Osteoporosis Therapy – A Review

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Abstract: Osteoporosis is a serious global health problem. It makes bones lose density and become weak over time, making fractures more common and imposing a huge economic burden on society. Risedronate sodium - is a common drug that is prescribed as a bisphosphonate for osteoporosis. However, it has extremely low oral bioavailability (<1%) due to not crossing the intestine very well, being eliminated quickly from the body, and binding strongly to dietary divalent cations. As a result, regular oral tablets fail to deliver the drug in an efficient and consistent way. Nanotechnology has provided new avenues for overcoming such barriers for poorly permeable medicines. Lipid-polymer hybrid nanoparticles (LPHNPs) are a contemporary nanocarrier platform that combines the predictable release and stability of polymeric nanoparticles with the friendliness and membrane touching properties of lipids. The polymer core contains the drug safely and prevents early interactions and the lipid layer around it enhances the adhesion to the intestinal wall and facilitates passage of the drug through cells. Recent studies demonstrate that LPHNPs can significantly improve a drug's stability, permeability and oral bioavailability. Despite these merits, risedronate is yet to be widely tried in LPHNPs. Developing risedronate loaded LPHNPs could thus be a valuable strategy for enhancing the oral absorption of this drug, thereby improving the drug's therapeutic effect, and propel the forward the nanotechnology-based osteoporosis treatments.

Keywords: Risedronate sodium; Lipid-polymer hybrid nanoparticles; Osteoporosis therapy; Oral drug delivery; Intestinal permeability enhancement

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. As a result, effective pharmaceutical therapy is required to prevent bone loss and lower fracture risk. Bisphosphonates are the most often used therapeutic medicines for osteoporosis. These medicines are pyrophosphate analogues that bind tightly to hydroxyapatite crystals in bone, inhibiting osteoclast-mediated bone resorption. Bisphosphonates minimize the risk of fractures by suppressing osteoclast activity and increasing bone mineral density. Nitrogen-containing bisphosphonates, such as alendronate, risedronate, ibandronate, and zoledronic acid, have proven significant clinical success in osteoporosis treatment [1, 2]. Among these, risedronate sodium is widely prescribed due to its potent antiresorptive activity and favorable safety profile. However, despite its therapeutic efficacy, risedronate exhibits extremely low oral bioavailability (approximately 0.6–0.7%), primarily due to its high polarity and limited permeability across intestinal membranes [3]. The negatively charged phosphonate groups of bisphosphonates remain ionized in the gastrointestinal tract,

restricting passive diffusion and resulting in less than 1% systemic absorption [4, 5]. Furthermore, risedronate readily forms complexes with divalent cations such as calcium and magnesium present in food, further reducing its absorption. Various formulation strategies, including enteric-coated tablets and gastro-retentive systems, have been investigated to improve risedronate delivery; however, these approaches do not sufficiently overcome the permeability barrier. Recently, nanotechnology-based drug delivery systems have shown potential for enhancing oral drug absorption. Among these, lipid-polymer hybrid nanoparticles (LPHNPs) combine the advantages of polymeric nanoparticles and lipid-based carriers, offering improved drug stability, controlled release, and enhanced membrane interaction. Their nanoscale size also facilitates intestinal uptake and improved drug permeability [6-8]. Therefore, the development of risedronate-loaded lipid-polymer hybrid nanoparticles represent a promising strategy to enhance intestinal permeability in osteoporosis therapy.

Literature Review

Several strategies have been studied in the attempt to improve the oral delivery of risedronate and other bisphosphonates. Conventional methods like enteric coated formulations, gastro retentive systems, delivery in different routes etc. have given moderate results in drug release and patient compliance. However, they have not effectively overcome the limitations of risedronate about its permeability. Recent developments in nanotechnology have been introducing a variety of nanocarrier systems. These include polymeric nanoparticles, liposomes and solid lipid nanoparticles, which improve drug stability and absorption. Among these systems, lipid-polymer hybrid nanoparticles (LPHNPs) have gained significant attention due to their core-shell architecture, combining polymer stability with lipid-mediated membrane interaction to enhance drug permeability and oral bioavailability.

Table 1. Comparison of Previous Studies with the Proposed Work

Study (Drug/System & Key Findings – Delivery Strategy and Limitation)	Risedronate Permeability Addressed	Nanocarrier-Based Delivery	Oral LPHNP Strategy	Ref
Risedronate formulations (tablets/spray): Conventional oral and sublingual delivery strategies reported very low bioavailability (<1%) due to permeability limitation; limitation includes poor systemic absorption or requirement of alternative administration route.	Yes	No	No	[2, 5, 9]
Chitosan nanoparticles / liposomes: Polymeric nanoparticle and liposomal delivery strategies improved encapsulation efficiency, drug stability, and mucoadhesion; limitation includes limited enhancement of intestinal permeability.	Yes	Yes	No	[10, 11]
Xyloglucan raft system: Gastroretentive drug delivery increased gastric residence time and drug release; limitation includes inability to significantly overcome permeability barrier.	Yes	No	No	[6]
Lipid–polymer hybrid nanoparticle: Hybrid nanocarriers integrate polymer stability with	No	Yes	Yes	[7, 8, 12, 13]

lipid-mediated membrane interaction to improve permeability; limitation includes limited clinical validation and scale-up challenges.				
Drug-loaded LPHNPs (acalabrutinib, posaconazole, thymoquinone): Hybrid nanoparticle delivery improved oral bioavailability (~3–5 fold) and intestinal permeability; limitation includes drug-specific formulation optimization and early-stage development.	No	Yes	Yes	[14-16]
Nanostructured lipid carriers / polymeric nanoparticles: Lipid or polymer nanoparticle delivery strategies improved drug solubility and targeted delivery; limitation includes lower structural stability or limited permeability enhancement.	No	Yes	No	[17, 18]
Hybrid nanocarriers: Lipid–polymer hybrid systems improved controlled drug release and intestinal uptake via membrane interaction and endocytosis; limitation includes formulation complexity and safety evaluation requirements.	No	Yes	Yes	[19, 20]
General nanocarrier systems: Lipid, polymeric, and multifunctional nanocarriers improved drug targeting and controlled release; limitation includes limited application to permeability-limited bisphosphonate drugs such as risedronate.	No	Yes	No	[21, 22]
This work – Risedronate-loaded LPHNPs: Proposed hybrid nanocarrier integrates polymeric drug protection with lipid-mediated permeability enhancement for oral delivery to overcome intestinal permeability limitation of risedronate.	Yes	Yes	Yes	This work

Conclusion

1. **Problem Statement Addressed / Motivation**

   The present study addresses the major limitation associated with risedronate sodium therapy, which is its extremely low oral bioavailability due to poor intestinal permeability and chelation with divalent cations in the gastrointestinal tract. Conventional oral formulations fail to overcome this permeability barrier, resulting in reduced systemic absorption and variability in therapeutic outcomes. Therefore, there is a need for an advanced drug delivery system capable of enhancing intestinal permeability and improving oral bioavailability of risedronate.

2. **Method Used / Proposed Strategy**

   To overcome these limitations, the study proposes the development of lipid-polymer hybrid nanoparticles for oral delivery of risedronate sodium. This hybrid nanocarrier system integrates the advantages of polymeric nanoparticles and lipid-based carriers, where the polymeric core

enables efficient drug encapsulation and controlled release, while the lipid shell enhances membrane interaction and permeability across intestinal epithelial cells.

3. **Key Findings**

   The literature analysis indicates that lipid–polymer hybrid nanoparticles have demonstrated significant potential in improving drug stability, permeability, and oral bioavailability of several poorly permeable drugs. The core-shell structure of LPHNPs provides enhanced drug protection, improved interaction with biological membranes, and controlled drug release. These characteristics suggest that risedronate-loaded LPHNPs could effectively overcome intestinal permeability barriers and improve therapeutic performance in osteoporosis treatment.

4. **Limitations and Future Work**

   Although lipid-polymer hybrid nanoparticles show promising advantages for oral drug delivery, their application in risedronate delivery remains limited and requires further investigation. Future studies should focus on formulation optimization, in vitro and ex vivo permeability evaluation to validate the effectiveness of the proposed system.

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