



**INTERNATIONAL JOURNAL OF  
PHARMACEUTICAL SCIENCES**  
[ISSN: 0975-4725; CODEN(USA): IJPS00]  
Journal Homepage: <https://www.ijpsjournal.com>



## Review Paper

# Impact of Nanoparticle Size and Concentration on the Release Profile and Pharmacokinetics of Proton Pump Inhibitors (PPIs): A Comprehensive Review

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## ARTICLE INFO

Published: 17 May, 2025

### Keywords:

Nanoparticle Size,  
Concentration, Release  
Profile, Pharmacokinetics,  
Proton Pump Inhibitors

### DOI:

10.5281/zenodo.15448392

## ABSTRACT

Proton pump inhibitors (PPIs) are widely prescribed for the treatment of acid-related gastrointestinal disorders, yet their clinical efficacy is often limited by poor solubility, acid-lability, and short systemic half-life. Nanoparticle-based drug delivery systems have emerged as a promising approach to overcome these limitations by enhancing drug stability, improving bioavailability, and enabling controlled release. Among the critical formulation parameters, nanoparticle size and concentration play pivotal roles in dictating the release profile, absorption kinetics, and overall pharmacokinetic behavior of PPIs. This comprehensive review explores the mechanistic influence of nanoparticle size and concentration on drug dissolution, mucosal penetration, systemic absorption, and metabolism of various PPI molecules, including omeprazole, lansoprazole, and dexlansoprazole. It also examines recent advancements in nanoformulation strategies, experimental outcomes, and in vivo pharmacokinetic data that underscore the potential of tailored nanoparticle systems in optimizing therapeutic outcomes. Furthermore, the review highlights current challenges, regulatory considerations, and future directions in designing nanoparticle-based PPI therapies with enhanced efficacy and safety. By integrating insights from nanotechnology, pharmaceutical sciences, and clinical pharmacokinetics, this review aims to guide future research and development efforts in the rational design of nano-enabled PPI formulations.

## INTRODUCTION

Proton pump inhibitors (PPIs) are a widely prescribed class of medications used to treat acid-

related gastrointestinal disorders, including gastroesophageal reflux disease (GERD), peptic ulcer disease, and Zollinger-Ellison syndrome. These drugs work by irreversibly inhibiting the

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Relevant conflicts of interest/financial disclosures: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.



H<sup>+</sup>/K<sup>+</sup>-ATPase enzyme (gastric proton pump) in the parietal cells of the stomach, leading to a profound and sustained reduction in gastric acid secretion [1]. Common PPIs include omeprazole, lansoprazole, esomeprazole, pantoprazole, and dexlansoprazole—each varying slightly in pharmacokinetic profile but sharing similar core mechanisms of action [2]. Despite their clinical effectiveness, PPIs suffer from significant biopharmaceutical limitations. Most PPIs are poorly water-soluble, which limits their dissolution and oral bioavailability [3]. Furthermore, they are highly acid-labile, meaning they degrade rapidly in the low pH environment of the stomach. This necessitates the use of enteric-coated formulations to protect the drug until it reaches the more neutral pH of the small intestine [4]. However, enteric coatings introduce their own challenges, such as delayed onset of action, variable absorption, and incomplete release. Additionally, PPIs have a short plasma half-life (typically 1–2 hours), which often requires repeated dosing to maintain effective acid suppression [5]. In recent years, nanoparticle-based drug delivery systems have emerged as a promising strategy to overcome these formulation challenges. Nanoparticles can improve the solubility, stability, and bioavailability of PPIs by increasing surface area, enhancing mucosal permeability, and protecting the drug from acidic degradation [6]. Nanocarriers such as solid lipid nanoparticles, polymeric nanoparticles, liposomes, and nanocrystals have been explored for their potential to enable controlled release, targeted delivery, and improved pharmacokinetic profiles of PPIs [7]. Among the critical formulation variables in nanoparticle design, particle size and concentration play pivotal roles in determining the release profile and pharmacokinetics of encapsulated drugs. Smaller nanoparticles typically exhibit higher surface area-to-volume ratios, resulting in faster dissolution

rates and improved cellular uptake, while larger particles may support more sustained release patterns [8]. Similarly, nanoparticle concentration can influence drug loading, release kinetics, mucosal interactions, and systemic exposure. Understanding the interplay between these parameters is crucial for the rational design of nanoformulations intended to optimize therapeutic outcomes of PPIs [9]. This review provides a comprehensive analysis of current research on how nanoparticle size and concentration affect the release behavior and pharmacokinetic performance of PPIs, with a focus on improving clinical efficacy, consistency, and patient adherence.

## 2. Fundamentals of Nanoparticles in Drug Delivery [10-21]

Nanoparticles are submicron-sized colloidal systems, typically ranging from 1 to 1000 nanometers, that serve as carriers for drug molecules. These carriers can enhance drug delivery by improving solubility, protecting unstable drugs from degradation, and enabling targeted or controlled release. In pharmaceutical applications, nanoparticles are especially valuable for drugs with poor aqueous solubility, short half-life, or low bioavailability—issues commonly associated with proton pump inhibitors (PPIs).

### 2.1 Types of Nanoparticles

Various types of nanoparticles have been developed for drug delivery, each offering unique structural and functional characteristics:

**Polymeric nanoparticles:** Comprised of biodegradable polymers such as PLGA (poly (lactic-co-glycolic acid)) or chitosan, these nanoparticles can provide controlled and sustained release profiles. Solid lipid nanoparticles (SLNs): Made from solid lipids, these systems offer excellent biocompatibility and are suitable for



lipophilic drugs like PPIs. Nanostructured lipid carriers (NLCs): Second-generation lipid nanoparticles combining solid and liquid lipids to improve drug loading and release behavior.

**Liposomes:** Phospholipid vesicles that encapsulate both hydrophilic and lipophilic drugs, commonly used for targeted delivery. Dendrimers and micelles: Branched and amphiphilic structures, respectively, that enhance drug solubility and improve biodistribution.

## 2.2 Role in Controlled Release and Targeted Delivery

Nanoparticles play a pivotal role in controlled release by allowing precise modulation of drug dissolution rates. Their small size and large surface area facilitate faster dissolution, while polymeric or lipid matrices can retard release for prolonged activity. In the case of PPIs, this can help maintain therapeutic plasma concentrations for extended periods, reducing the need for frequent dosing. Moreover, nanoparticles can be engineered for targeted delivery, where surface modification (e.g., with ligands or antibodies) enables site-specific accumulation. This is particularly beneficial for PPIs when mucosal targeting or intracellular delivery is required to bypass degradation pathways.

## 2.3 Mechanisms by Which Size and Concentration Influence Performance

Two critical physicochemical parameters—nanoparticle size and concentration—directly affect the performance of nanoparticle-based drug delivery systems:

**Size:** Smaller nanoparticles offer a larger surface area-to-volume ratio, leading to enhanced dissolution rates and better mucosal penetration. Size also impacts cellular uptake, with particles under 200 nm often demonstrating better

endocytosis and bioavailability. However, very small sizes may lead to faster clearance or toxicity.

**Concentration:** Higher nanoparticle concentrations can increase drug payload and therapeutic effect but may also result in particle aggregation, increased viscosity, or cytotoxicity if not well-optimized. Additionally, the concentration influences the release kinetics, where high drug loading may delay release due to saturation of diffusion pathways.

## 3. Influence of Nanoparticle Size on Drug Delivery Performance [22-31]

Nanoparticle size is a critical determinant in the design and performance of drug delivery systems, particularly for orally administered drugs like proton pump inhibitors (PPIs). The physical dimensions of nanoparticles directly affect their dissolution rate, absorption, mucosal interaction, and cellular uptake, all of which influence the release profile and pharmacokinetics of the encapsulated drug.

### 3.1 Small Nanoparticles (typically <200 nm)

Smaller nanoparticles possess a higher surface area-to-volume ratio, which leads to faster dissolution rates—an essential property for improving the solubility of poorly water-soluble drugs like PPIs. This rapid dissolution can result in enhanced absorption in the gastrointestinal (GI) tract, particularly in the upper small intestine where PPIs are preferentially absorbed. Additionally, smaller particles have shown superior cellular uptake via endocytosis, especially in intestinal epithelial cells, improving bioavailability and systemic exposure. Their small size also facilitates mucosal penetration, allowing the particles to diffuse through the mucus layer and reach the epithelial surface more effectively. However, excessively small nanoparticles (<50 nm) may be susceptible to rapid clearance,



aggregation, or cytotoxicity, which necessitates careful optimization of size for safe and effective delivery.

### 3.2 Larger Nanoparticles (typically >200–400 nm)

Larger nanoparticles tend to release drugs more slowly, making them suitable for sustained-release formulations. This can be advantageous for PPIs, which have a short plasma half-life, as prolonged release may maintain therapeutic levels over extended periods. Despite this benefit, larger nanoparticles generally demonstrate reduced mucosal penetration and lower intracellular uptake. They may also be more vulnerable to enzymatic degradation or acid-mediated destabilization in the harsh GI environment, especially without protective coatings. This limits their effectiveness in bypassing gastric degradation—one of the primary challenges in PPI formulation.

### 3.3 Impact on Drug Release Kinetics

Nanoparticle size has a profound influence on drug release kinetics. Smaller particles often display burst release due to the rapid dissolution of surface-associated drug, whereas larger particles can exhibit sustained or biphasic release patterns depending on matrix composition and drug distribution.

### 3.4 Mucosal Penetration

Studies show that nanoparticles under 200 nm are better able to diffuse through intestinal mucus and reach absorptive surfaces, which is crucial for enhancing the bioavailability of PPIs. Larger particles tend to be trapped in mucus or removed by peristalsis before reaching the epithelium.

### 3.5 Stability in the GI Tract

Smaller nanoparticles, particularly those made of lipid-based or polymeric carriers, may offer greater protection to acid-labile PPIs by encapsulating them in a pH-responsive matrix, thereby enhancing gastric stability. However, stability is also influenced by other formulation factors such as surface charge, hydrophobicity, and use of enteric coatings.

### 3.6 Intracellular Uptake and Transport

Particle size modulates the mechanism and extent of cellular internalization. Nanoparticles in the range of 50–200 nm are typically internalized via clathrin-mediated endocytosis, which is efficient for drug transport across intestinal epithelia. In contrast, larger particles are often excluded or retained extracellularly.

## 4. Analytical Techniques for Characterization [32]

- **Particle size analysis:** Dynamic light scattering (DLS), scanning electron microscopy (SEM), transmission electron microscopy (TEM).
- **Drug release studies:** Dialysis bag method, USP dissolution apparatus with simulated gastric/intestinal fluids.
- **Pharmacokinetic analysis:** HPLC or LC-MS/MS assays for plasma concentration measurement following oral administration in animal models or clinical trials.

## 5. Clinical Implications

Optimizing nanoparticle size and concentration can significantly improve the clinical efficacy of PPI therapies. Formulations with finely tuned characteristics can offer:

- Enhanced bioavailability.
- Reduced dosing frequency.



- Improved patient compliance.
- Lower risk of side effects, especially with chronic use.

Furthermore, nanoformulations may offer new therapeutic avenues such as targeted delivery to *Helicobacter pylori*-infected gastric tissues. From a regulatory standpoint, the critical quality attributes (CQAs) of nanoparticle formulations, including size distribution and drug content uniformity, must be strictly controlled to ensure safety and efficacy.

## 6. Challenges and Future Perspectives

Despite the promise of nanoparticle-based PPI delivery, several challenges remain:

- Stability issues during storage and transit through the gastrointestinal tract.
- Scale-up difficulties for large-scale manufacturing.
- Regulatory hurdles related to nanoparticle safety and biodistribution.

Future research should focus on stimuli-responsive nanoparticles, targeted delivery systems, and personalized medicine approaches to maximize the therapeutic potential of PPIs.

## CONCLUSION

Nanoparticle size and concentration are critical determinants of the release profile and pharmacokinetics of proton pump inhibitors (PPIs). Smaller particle sizes typically enhance dissolution rates and promote more efficient absorption, thereby improving bioavailability. Conversely, optimal nanoparticle concentration is essential to achieve sustained drug release while minimizing aggregation-related challenges that could compromise therapeutic performance. A comprehensive understanding of the interplay between particle size and concentration will facilitate the rational design of next-generation

nanoformulations for PPIs, offering improved clinical efficacy, reduced dosing frequency, and enhanced patient outcomes.

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**HOW TO CITE:** Tanu Shri Biswas\*, Impact of Nanoparticle Size and Concentration on the Release Profile and Pharmacokinetics of Proton Pump Inhibitors (PPIS): A Comprehensive Review, *Int. J. of Pharm. Sci.*, 2025, Vol 3, Issue 5, 2809-2815. <https://doi.org/10.5281/zenodo.15448392>