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Effectiveness of Nanoparticle-Based Drug Delivery Systems in Enhancing Oral Bioavailability: A Systematic Review

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Systematic Review

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Abstract

Background

Oral administration is the preferred route for drug delivery due to convenience and patient compliance, yet its efficacy is hampered by low solubility and enzymatic degradation. Nanoparticulate drug delivery systems (NDDS) have emerged as a strategic solution to overcome these gastrointestinal (GI) barriers.

Objective

To systematically evaluate the impact of nanoparticle-based drug delivery systems on enhancing oral bioavailability (BA).

Methods

A systematic literature search was conducted using databases such as PubMed and Google Scholar following PRISMA guidelines. Studies comparing NDDS to conventional formulations using pharmacokinetic parameters (AUC, Cmax) were prioritized.

Results

The review identifies that nanoparticles (NPs) consistently improve oral BA, with improvements ranging from 2-fold to over 40-fold depending on the drug and carrier type.

Conclusion

NDDS represent a robust technology for improving the BA of poorly soluble drugs, though clinical translation remains the primary challenge

Introduction to oral route of drug administration

The oral route is the most common and widely preferred route for drug delivery due to its significant advantages in patient compliance, convenience, and non-invasiveness(1,2). It represents approximately 90% of the global market share of pharmaceutical formulations intended for human use, with nearly 84% of the best-selling drug products being administered via this route. Beyond its patient-friendly nature, the oral route is cost-effective and allows for the ease of large-scale manufacturing of various dosage forms like tablets and capsules(1). Furthermore, oral delivery can be utilized both for the localized treatment of gastrointestinal pathological conditions, such as inflammatory bowel disease or colorectal cancer, and for achieving systemic therapeutic effects through intestinal absorption(1–4)

Challenges of Oral Drug Delivery

Despite its dominance, the development of oral formulations is hampered by a complex "bioavailability barrier network" that severely limits the systemic exposure of many therapeutic agents and achieving therapeutic systemic concentrations is often hampered by hostile gastrointestinal (GI) environments, including extreme pH fluctuations (pH 1.2–8.0), proteolytic enzymes (pepsin, trypsin), and the physical barrier of the intestinal mucus layer(1,5).

Furthermore, approximately 40% of new chemical entities (NCEs) are poorly water-soluble (BCS Class II and IV), leading to erratic dissolution and low bioavailability (BA)(1,6,7). Nano particulate drug delivery systems (NDDS)—ranging from 10 to 1000 nm—offer a transformative solution by protecting drugs from premature degradation, increasing surface area for dissolution, and facilitating specialized transport pathways such as M-cell mediated lymphatic uptake, which bypasses hepatic first-pass metabolism(1–3,8).

Defining Bioavailability and the BCS Framework

Bioavailability is dictated by the rate and extent of drug absorption, which is largely governed by solubility, dissolution rate, and intestinal permeability. To predict a drug's performance, the Biopharmaceutics Classification System (BCS) categorizes substances into four classes(9–12):

- **Class I:** High solubility, high permeability (well-absorbed).
- **Class II:** Low solubility, high permeability (dissolution-limited).
- **Class III:** High solubility, low permeability (permeability-limited).
- **Class IV:** Low solubility, low permeability (very poor bioavailability).

Current data indicate that approximately 40% of new chemical entities (NCEs) and 70% of novel medications exhibit low aqueous solubility, placing them in BCS Class II or IV(7,11). For these compounds, reaching therapeutic concentrations in systemic circulation is difficult due to erratic dissolution and poor membrane penetration(7,13)

Nanotechnology as a Strategic Solution for Oral Delivery

Nanoparticulate drug delivery systems (NDDS) have emerged as a revolutionary strategy to surmount GI barriers and improve oral bioavailability(2,13). Nanocarriers are defined as solid or liquid particles with diameters ranging from 10 to 1000 nm(13,14). These systems can be formulated using biocompatible and biodegradable materials such as synthetic polymers (PLGA, PCL), natural polymers (chitosan, albumin), or lipids (fatty acids, phospholipids)(8,13,15). Common nano-architectures include nanosuspensions, polymeric micelles, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC). By encapsulating active agents, NDDS protect them from premature degradation, increase intracellular penetration, and ensure a more uniform distribution in the GI tract, which reduces local irritation(2,13,14)

Methods

Study Design

This systematic review was designed to evaluate the quantitative impact of various nanocarriers on the oral BA of diverse therapeutic agents compared to conventional formulations.

Search Strategy

Systematic searches were conducted across databases including **PubMed, Scopus, Web of Science, and Google Scholar**. Keywords utilized included “nanoparticles,” “oral bioavailability,” “pharmacokinetics,” and “drug delivery systems”.

Inclusion Criteria

- In vivo studies (animal models or human subjects).
- Direct comparison between nanoparticle formulations and conventional controls (e.g., suspensions, solutions, or commercial products).
- Reporting of key pharmacokinetic (PK) parameters: AUC (Area Under the Curve), Cmax, and Tmax.

Exclusion Criteria

- In vitro only studies without animal/human validation.
- Review articles, editorials, or conference abstracts lacking original data.
- Studies with incomplete PK data (e.g., missing standard deviations).

Data Extraction

A standardized extraction protocol was used to collect the drug name, nanocarrier’s type, experimental model, and the fold-increase or percentage enhancement in BA.

Quality Assessment

Methodological quality was assessed based on standardized risk-of-bias frameworks for preclinical studies (e.g., SYRCLE) to ensure data integrity and reproducibility.

Results

PRISMA Flow Description

The selection process followed PRISMA guidelines, typically involving the initial identification of records, removal of duplicates, and screening of titles and abstracts to exclude irrelevant delivery routes. Eligible full-text articles were then assessed for specific PK data availability.

Study Characteristics and Effects on Oral Bioavailability

The table below summarizes representative data extracted from the selected research papers.

Drug Name	Country	Nanocarrier Type	Experimental Model	BA Enhancement / Key Outcome	Key Results/Findings	Reference
Asenapine maleate	India	Solid Lipid NPs (SLN)	Rats	50.2-fold	Enhanced absorption via TPGS-stabilized lymphatic uptake.	(16)
Indinavir	Israel	Nanoparticle-in-Microparticle	Mongrel Dogs	47-fold	Nanonization increased dissolution; half-life rose from 0.8h to 22h.	(4)
Puerarin	China	Solid Lipid NPs (SLN)	Rats	43-fold	Shorter Tmax and rapid absorption compared to suspension.	(3)
Apomorphine	Taiwan	Solid Lipid NPs (SLN)	Rats	13-fold	Significant improvement in systemic exposure for CNS therapy.	(5)
Daidzein	China	Lipid Nanocarriers	Rats	At least 10-fold	Complexation with phospholipids significantly boosted blood levels.	(17)
Probucol	China	Porous Starch Nanodelivery	Rats	~10-fold	Self-assembled system improved absorption of highly lipophilic drug.	(17)
Doxorubicin	India	PEGylated SLNs	Rats	7.5-fold	Surface modification (PEG) avoided RES uptake, prolonging circulation.	(5,13)
Curcumin	China	PLGA Nanoparticles	Rats	5.6-fold	Increased water solubility (640-fold) led to longer half-life.	(3,18)
Quercetin	USA	Solid Lipid NPs (SLN)	Rats	5.7-fold (571%)	Relative BA greatly improved compared to standard suspension.	(14)
Ramipril	India	Nanoemulsions (o/w)	Rats	5.4-fold (539%)	Significant enhancement over both suspension and capsule forms.	(3)
Tacrolimus	Israel	PMA Nanoparticles	Rats	4.9-fold	Double coating with PMA polymers	(14)

					improved GI stability.	
Compound 301029	USA	Nanonized drug	Mice	4.5-fold (449%)	Increased surface area/dissolution per Noyes-Whitney equation.	(7)
Cyclosporine A	China	pH-sensitive (Eudragit S100)	Rats	132.5% vs Neoral	Highest AUC achieved via targeted intestinal release.	(19,20)
Insulin	Portugal	Chitosan-coated SLNs	Rats	17% relative BA	Mucoadhesion prolonged residence; significant boost from 2% (free).	(16)

Discussion

The data extraction demonstrates that nanoparticle-based drug delivery systems consistently and significantly enhance oral bioavailability across a diverse range of chemical entities. The magnitude of improvement—ranging from 2-fold to over 50-fold—is primarily driven by three synergistic mechanisms:

1. Improved Solubilization: Nanonization increases the effective surface area and curvature of drug particles, which, according to the Noyes-Whitney equation, accelerates dissolution rates and saturation solubility(7,19).
2. Bypassing First-Pass Metabolism: Lipid-based carriers (SLNs, SMEDDS) leverage physiological fat-absorption pathways, directing drugs through the lymphatic system via Peyer’s patches, thereby avoiding hepatic degradation(8,16).
3. Enhanced Permeability and Protection: Polymeric matrices (e.g., PLGA, Chitosan) act as a physical shield against enzymatic hydrolysis(1,21). Furthermore, surface modifications like PEGylation or mucoadhesive coatings increase the residence time and reduce clearance by the intestinal mucus layer(16,22,23)

Despite the overwhelming preclinical success reported in animal models, clinical translation remains limited(16,17). The review highlights that while nanosuspensions and self-emulsifying systems have reached the market, more complex architectures like dendrimers and inorganic nanoparticles face hurdles in large-scale manufacturing, long-term stability, and clear regulatory guidelines for human safety(2,3,22).

Synthesis of Findings

The compiled evidence highlights that nanoparticle encapsulation is a superior strategy for surmounting the bioavailability bottlenecks of modern pharmaceuticals. Lipid nanocarriers (SLNs/NLCs) emerge as particularly potent for lipophilic compounds, with asenapine and puerarin showing extraordinary enhancements (>40-fold) through lymphatic bypass. Polymeric systems provide significant, though often more moderate, gains (2–10 fold) by providing precise pH-responsive release and protection for labile peptides like insulin. The transition from BCS Class II/IV limitations to therapeutic efficacy is clearly size-dependent, with particles below 200–300 nm showing optimal GI transit and uptake. Collectively, these findings suggest that while NDDS technology is highly effective, future research must prioritize standardizing human trial models to bridge the gap between preclinical promise and clinical application.

Limitations:

- **Study Variability:** There is high heterogeneity in study designs, animal models, and dosages, making direct comparisons difficult.
- **Lack of Human Trials:** Despite vast animal data, very few oral nanocarriers have reached clinical trials or the market due to concerns over large-scale manufacturing and safety

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Figures

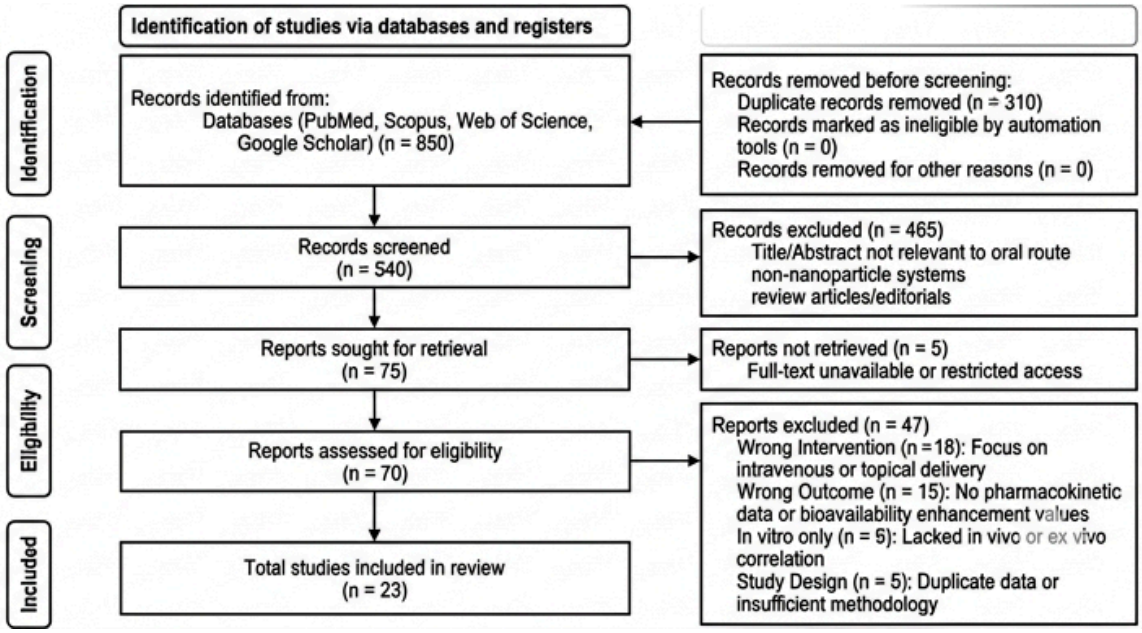


Figure 1

Unnumbered image in Results section.