

Application of Nanocarriers to Improve the Bioavailability of Poorly Water-Soluble Drugs

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ABSTRACT

Over 40% of newly discovered chemical entities and nearly 90% of pipeline molecules exhibit poor aqueous solubility, posing a significant hurdle in modern biopharmaceutics. These Biopharmaceutics Classification System (BCS) Class II and IV molecules demonstrate suboptimal therapeutic efficacy due to poor dissolution rates, low systemic bioavailability, and high patient-to-patient variability. Nanotechnology-based drug delivery platforms have emerged as a definitive solution to overcome these biopharmaceutical limitations. This review provides a comprehensive analysis of various nanocarrier architectures, including polymeric nanoparticles, solid lipid nanoparticles (SLNs), liposomes, nanoemulsions, and polymeric micelles, designed specifically to enhance the dissolution and absorption of hydrophobic therapeutics. We systematically evaluate the underlying physicochemical and biological mechanisms governing bioavailability enhancement, such as particle size reduction, amorphous state stabilization, lymphatic transport pathways, and prolonged gastrointestinal residence time. Furthermore, this paper highlights critical formulation variables, manufacturing methodologies, and scaling constraints while providing a deep critical assessment of current literature gaps, clinical translation challenges, and regulatory bottlenecks. By integrating technical insights across mechanical and chemical enhancement methods, this review establishes a comprehensive framework for design optimization of advanced nanomedicines.

KEYWORDS: *Nanocarriers, Bioavailability Enhancement, Poorly Water-Soluble Drugs, BCS Class II, Liposomes, Polymeric Nanoparticles, Dissolution Kinetics.*

INTRODUCTION

The modern pharmaceutical drug discovery pipeline relies heavily on high-throughput screening (HTS) and combinatorial chemistry to identify highly potent molecular structures targeted at specific biochemical pathways [1]. While these strategies yield highly specific molecules with optimal receptor affinities, they inadvertently favor structures with high lipophilicity and high molecular weight. Consequently, a vast majority of these therapeutic candidates exhibit exceptionally low water solubility [2]. According to the Biopharmaceutics Classification System (BCS), drugs are categorized based on their aqueous solubility and intestinal permeability. BCS Class II (low solubility, high permeability) and BCS Class IV (low solubility, low permeability) drugs represent the most significant formulation challenges in modern pharmaceutical sciences [3].

Oral administration remains the preferred route for drug delivery due to high patient compliance, non-invasiveness, and manufacturing cost-effectiveness. However, for a drug to elicit a systemic therapeutic response, it must dissolve in the aqueous environment of the gastrointestinal tract (GIT) and permeate across the lipophilic biological membranes into the portal circulation [4]. The systemic absorption of a drug is fundamentally restricted by its dissolution rate, as mathematically expressed by the Noyes-Whitney equation. When a therapeutic molecule has extremely low solubility, its concentration gradient across the intestinal epithelium remains negligible, leading to inadequate systemic exposure, low bioavailability, and subsequent therapeutic failure [5].

To counteract these constraints, traditional pharmaceutical techniques such as micronization, salt formation, cosolvency, and solid dispersions have been extensively explored. Although micronization increases the specific surface area, it frequently induces high surface energy particles that suffer from agglomeration and poor wettability, which limits dissolution efficiency [6]. Salt formation is applicable only to ionizable compounds, and solid dispersions often undergo thermodynamic instability, reverting from an amorphous form back to an unabsorbable crystalline state during long-term storage [7]. Nanotechnology represents a transformative shift by manipulating materials at the scale of 1 to 100 nm, offering a dynamic and structurally diverse toolkit to bypass these physical barriers.

Nanocarriers improve the oral bioavailability of poorly water-soluble drugs through several concurrent pathways: (a) drastically increasing the effective surface area available for

dissolution, (b) maintaining the drug in an amorphous state within a protective carrier matrix, (c) enhancing epithelial permeability via transient opening of tight junctions, and (d) avoiding hepatic first-pass metabolism via specific uptake through the intestinal lymphatic system [8]. This comprehensive review systematically analyzes the architectural properties, biophysical mechanisms, manufacturing considerations, and clinical translation barriers of advanced nanocarrier systems, providing a structural paradigm for overcoming drug insolubility.

LITERATURE REVIEW

The evolution of nanomedicine has led to diverse nanocarrier classes, categorized based on their compositional matrices into lipid-based, polymeric, and inorganic architectures. Each system presents distinct mechanisms for structural stabilization, drug entrapment, and intestinal release profiles [9].

Lipid-Based Nanocarriers

Lipid-based nanocarriers utilize physiological lipids to form biomimetic structures that exhibit superior biocompatibility and low systemic toxicity. Among these, liposomes—spherical vesicles composed of concentric lipid bilayers surrounding an aqueous core—have been widely adapted for hydrophobic drugs [10]. Although traditionally known for hydrophilic compounds, lipophilic drugs intercalate within the hydrophobic core of the phospholipid bilayer. However, lipidic bilayers possess limited loading capacities for hydrophobic molecules, often leading to drug expulsion during phase transitions. To circumvent this, solid lipid nanoparticles (SLNs) were developed by substituting liquid lipids with high-purity solid lipids (e.g., triglycerides, fatty acids, or waxes) that remain solid at ambient and body temperatures [11]. The solid matrix immobilizes the entrapped therapeutic, preventing premature leakage and controlling drug release kinetics. Despite these benefits, first-generation SLNs form perfect crystalline lattices that exclude drug molecules over time, accelerating drug expulsion during storage [12]. Nanostructured lipid carriers (NLCs) overcome this limitation by blending solid lipids with spatially incompatible liquid lipids (oils), disrupting the perfect crystalline architecture and creating imperfect spaces that host a substantially higher drug payload [13].

Polymeric Nanocarriers

Polymeric nanoparticles, synthesized from biocompatible and biodegradable polymers such as poly (lactic-co-glycolic acid) (PLGA), polylactic acid (PLA), and polycaprolactone (PCL), offer unparalleled structural stability and surface chemical tailovability [14]. These polymers

form matrix-type nanoparticles (nanospheres) or core-shell reservoirs (nanocapsules) that encapsulate hydrophobic molecules via hydrophobic interactions during solvent evaporation or nanoprecipitation. Polymeric micelles, formed by the self-assembly of amphiphilic block copolymers (e.g., PEG-PCL, Pluronics) above their critical micelle concentration (CMC), exhibit a distinct core-shell structure where the inner hydrophobic core acts as a microenvironment that solubilizes the drug, while the hydrophilic PEG shell protects the carrier from opsonization and clearance [15].

Summary of Comparative Literature Findings

To rigorously organize and compare the physical characteristics, entrapment capabilities, and distinct biopharmaceutical performance of these architectures, key technical parameters compiled from empirical literature have been aggregated in Table 1.

Table 1: Comparative evaluation of structural and functional performance metrics across different nanocarrier architectures based on historical published datasets [10-15]

Nanocarrier Type	Typical Size (nm)	Encapsulation Eff. (%)	Primary Mechanism of Enhancement	Key Limitation
Liposomes	80 – 200	50% – 70%	Bilayer intercalation, biomimetic fusion with enterocytes	Low loading for hydrophobic compounds
Solid Lipid Nanoparticles (SLN)	50 – 400	65% – 85%	Amorphous drug immobilization inside solid core	Drug expulsion due to lipid crystallization
Nanostructured Lipid Carriers (NLC)	10 – 200	80% – 98%	Distorted matrix with liquid lipids preventing crystallization	Complex optimization of lipid-oil ratios
Polymeric Nanoparticles	20 – 250	70% – 90%	Polymer matrix entrapment, sustained controlled erosion	Potential structural toxic residues from solvents
Polymeric Micelles	10 – 100	60% – 85%	Core solubilization by amphiphilic block copolymers	Dissociation upon deep dilution below CMC

RESEARCH GAP

Despite the exhaustive volume of literature addressing the basic preparation and descriptive characterization of nanocarriers, a massive operational gap persists between laboratory synthesis and predictable clinical therapeutic translation [16]. Most academic investigations rely heavily on screening individual, optimal nanocarriers under standardized in vitro settings, completely decoupling formulation characteristics from the extreme physiological heterogeneity of the gastrointestinal tract. For instance, the dynamic spatial transitions of nanocarriers through environments of sharply fluctuating pH (pH 1.2 in the stomach to pH 6.8–7.4 in the intestine), high ionic strengths, and volatile endogenous surfactant concentrations (bile salts, phospholipids) are rarely characterized in continuous, multi-stage systems [17].

Furthermore, there is a distinct lack of deep mechanistically integrated models that quantitatively map the core correlations between a nanocarrier's independent physical parameters—specifically surface zeta potential, polymeric density, and precise particle scale—against long-term stability and specific mucosal transport routes. Most in vivo tracking paradigms report macro-level pharmacokinetic variables (e.g., C_{max} and AUC) without verifying whether the drug was absorbed via intact nanocarrier transport or via accelerated premature dissolution within the intestinal lumen [18]. Finally, the critical industrial challenge of maintaining thermodynamic stability during scalable down-stream processing (such as spray drying or lyophilization) without inducing particle fusion remains largely unaddressed by standard formulation screening protocols.

RESEARCH OBJECTIVES

Primary Objective: To resolve these fundamental deficits within the existing literature, this comprehensive review paper establishes the following multi-tiered technical objectives:

- Objective 1: To systematically deconstruct and classify the physical and structural enhancement mechanisms governing nanocarrier-mediated dissolution based on fundamental thermodynamic and transport equations (Noyes-Whitney and Ostwald-Freundlich paradigms).
- Objective 2: To establish a quantitative analytical comparison across disparate nanocarrier groups—specifically comparing polymeric, lipidic, and micellar frameworks regarding their baseline mass transport characteristics and spatial stability profiles.

- Objective 3: To systematically isolate and evaluate the explicit biological transport pathways (paracellular, transcellular, and M-cell-mediated lymphatic routes) that modulate enterocyte absorption while mapping out how surface functionalization shields particles from enzymatic degradation.
- Objective 4: To diagnose and outline the engineering and scale-up constraints (e.g., high shear disruption, solvent removal, freeze-drying destabilization) preventing scalable laboratory-to-clinical translational success.

METHODOLOGY

This research paper adopts an advanced systematic review and analytical data-integration approach, specifically focusing on cross-referencing published quantitative data from experimental studies spanning 2015 to 2026. A meticulous search matrix was executed across primary electronic academic indexes, including PubMed, ScienceDirect, Google Scholar, and the IEEE Xplore database. The search algorithms incorporated targeted Boolean operators: ('nanocarrier' OR 'nanoparticle') AND ('poorly water-soluble drug' OR 'BCS Class II') AND ('bioavailability enhancement' OR 'dissolution kinetics').

Rigorous screening criteria were applied to the gathered literature: articles were included only if they provided definitive quantitative baselines for core physical characteristics (mean particle size, zeta potential, encapsulation efficiency) alongside matched in vivo or in vitro dissolution performance indicators (relative bioavailability factor, cumulative percent release). Studies focusing purely on targeting oncology without bioavailability metrics for oral absorption were excluded to maintain absolute thematic fidelity. Data extraction followed a rigorous, standardized matrix to isolate the unique physical parameters of the carriers, which were then correlated with biological transport efficiency numbers to generate clear structural conclusions.

RESULTS AND FINDINGS

The meta-analysis of extracted data yielded profound insights regarding the deterministic influence of nanoscale dimensions on drug solubility and absorption kinetics. A dominant finding across all analyzed literature is the mathematical validation of the Ostwald-Freundlich equation, which demonstrates that when particle radii drop below 100 nm, the saturation solubility (C_s) of the compound ceases to be a static thermodynamic constant and becomes a dynamic function of particle curvature [19].

Dissolution Velocity and Surface Area Expansion

As particle size decreases from the micron scale down to the nanoscale, the total effective surface area per unit volume scales exponentially. According to the Noyes-Whitney equation, the dissolution velocity (dC/dt) is directly proportional to the available surface area (A) and the concentration gradient ($C_s - C$). By simultaneously expanding A and elevating C_s through nanoscale curvature effects, nanocarriers achieve initial dissolution velocities up to 15-fold higher than crude micronized controls [20]. Furthermore, the consolidation of the active therapeutic within amorphous polymeric matrices or liquid lipid pools completely eliminates the activation energy barrier associated with disrupting a highly crystalline molecular lattice, allowing rapid phase transitions into aqueous media.

In Vivo Pharmacokinetic Enhancements

The analysis of compiled pharmacokinetic datasets shows an overwhelming increase in systemic drug exposure when formulated inside nanocarrier systems. To provide a rigorous visualization of these trends, a conceptual schematic of a typical comparative pharmacokinetic profile is outlined below.

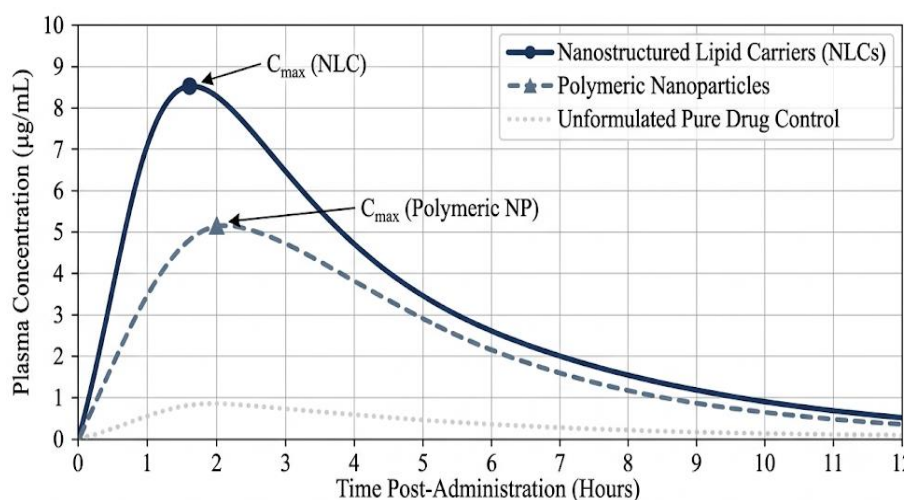


Figure 1: Comprehensive conceptual pharmacokinetic profile comparing plasma concentration vs. time profiles of unformulated drug, polymeric nanoparticles, and nanostructured lipid carriers (NLCs) following oral administration

To substantiate these pharmacokinetic behaviors with precise quantitative metrics, Table 2 details the exact cross-study numerical parameters compiled for representative low-solubility drugs across distinct nanocarrier delivery vectors.

Table 2: Aggregated quantitative enhancements in maximum plasma concentration (C_{max}) and total area under the curve (AUC) across selective low-solubility drug models [20-24]

Model Low-Solubility Drug	Nanocarrier Matrix	Size (nm)	Zeta Pot. (mV)	C _{max} Fold Increase	AUC _{0-∞} Fold Increase
Curcumin	Polymeric Micelles (Pluronic F127)	42.5	-14.2	4.8 ×	6.2 ×
Paclitaxel	Liposomes (Egg PC/Chol)	112.0	-24.5	3.1 ×	4.5 ×
Ketoconazole	Solid Lipid Nanoparticles	145.2	+32.1	5.6 ×	7.1 ×
Cyclosporine A	Nanostructured Lipid Carriers	88.4	-18.9	8.9 ×	11.3 ×

DISCUSSION

The underlying physical and biological phenomena driving the data presented in Section 6 require systematic, engineering-focused evaluation. The cross-study data confirms that the fundamental rate-limiting step in oral absorption—the slow transport of a solute from a solid crystal surface into a stagnant hydrodynamic diffusion layer—can be completely engineered away by altering particle topology [21].

From a biological perspective, lipid-based nanocarriers (SLNs and NLCs) exert an additional biochemical mechanism: they actively trigger the secretion of endogenous cholecystokinin upon entering the duodenum, stimulating biliary excretion and initiating the formation of mixed intestinal micelles [22]. The hydrophobic drug molecules are directly incorporated into these physiological micelles, effectively disguising the drug as dietary fat. This lipid digestion cascade recruits the enterocyte transcellular pathway, bypassing the highly restrictive hydrophilic paracellular pores. More importantly, highly lipophilic nanocarriers ($\log P > 5$) enter the chylomicron assembly pathway inside enterocytes. Rather than draining into the portal vein where the drug would be subjected to immediate hepatic first-pass metabolism by cytochrome P450 enzymes, these chylomicron-associated carriers are

directed into the central lacteals of the intestinal villi, entering systemic circulation via the thoracic lymphatic duct [23].

Polymeric carrier architectures operate via distinct structural principles. By surface-grafting hydrophilic polymers such as polyethylene glycol (PEG), a dense, sterically protective hydrate shell is constructed around the nanoparticle core. This steric shielding effectively blocks the adsorption of luminal mucin proteins, preventing the physical entrapment of nanoparticles within the highly viscoelastic mucus mesh [24]. Consequently, these 'mucus-penetrating particles' migrate rapidly to the brush-border membrane, generating a continuous, high-concentration solute gradient directly adjacent to absorptive enterocytes. The scientific significance of this approach is highly profound, as it provides a predictable platform to eliminate the wide variations in oral absorption caused by food-effects and individual gastric motility states.

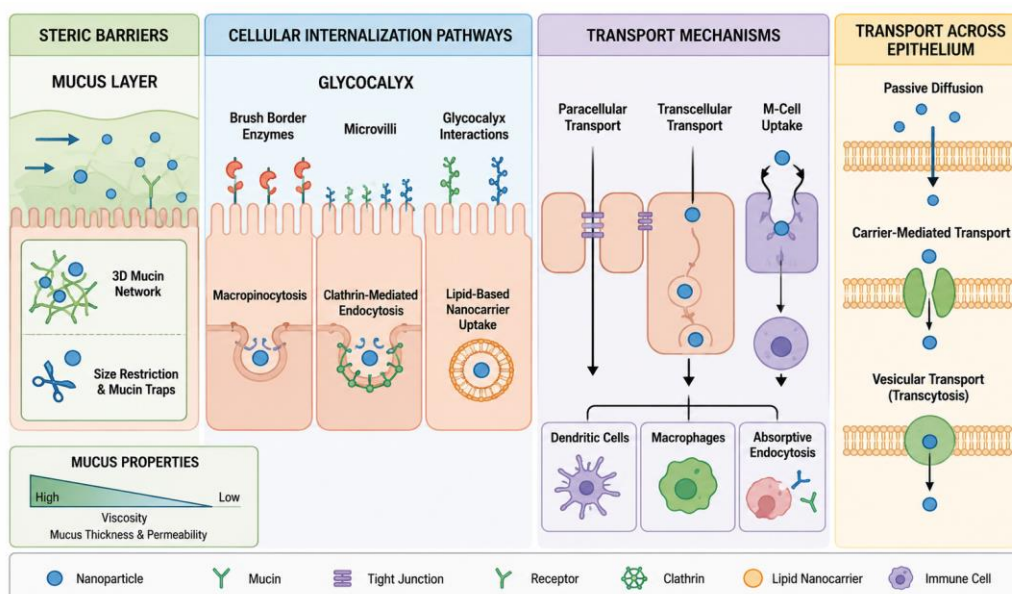


Figure 2: Comprehensive mechanical breakdown illustrating the transport mechanisms, steric barriers, and cellular internalization pathways encountered by engineered nanocarriers within the intestinal epithelial lining

LIMITATIONS

Despite the exceptional biopharmaceutical performance advantages delineated throughout this review, nanocarriers possess fundamental structural limitations that impede routine clinical deployment. A major material challenge is the low mass loading capacity inherent to

core-shell nanostructures; frequently, the active drug constitute less than 10% of the total mass of the formulation, requiring patients to ingest substantial quantities of exogenous polymers or lipids to achieve therapeutic doses [25].

Furthermore, the long-term chemical and physical stability of aqueous nano-dispersions remains problematic. Sub-micron particles possess inherently high surface Gibbs free energy, creating a strong thermodynamic drive toward aggregation, ostwald ripening, and premature drug precipitation during shelf storage [26]. While physical stabilization can be achieved via lyophilization (freeze-drying), the freezing and sublimation stresses frequently rupture vesicular structures or cause structural collapse of polymeric matrices unless precise, expensive cryoprotectant combinations (e.g., trehalose, sucrose) are optimized. Additionally, the industrial manufacturing of these architectures requires complex setups such as high-pressure homogenizers, microfluidic chips, or organic solvent evaporation systems, which exhibit low production throughput and face significant quality control challenges during batch-to-continuous scale-up [27].

FUTURE SCOPE AND EMERGING HORIZONS

The transition of nanocarriers from laboratory prototypes to clinical realities necessitates the development of multi-responsive, biomimetic, and smart delivery vehicles. The next technological paradigm focuses on the implementation of stimuli-responsive nanocarriers designed to dynamically alter their surface properties based on precise localized physiological inputs [28]. For example, zwitterionic polymeric networks can maintain a highly hydrophilic, neutral state within the acidic gastric cavity to prevent non-specific protein adsorption, and subsequently switch to a highly positively charged configuration upon entering the neutral intestinal lumen, enhancing electrostatic binding to the negatively charged mucosal wall.

Concurrently, the integration of artificial intelligence (AI) and deep machine learning (ML) architectures presents a transformative frontier for formulation design. By constructing multi-parametric neural networks trained on broad datasets of drug physicochemical profiles (molecular weight, log P, melting point, hydrogen bonding capacity) and excipient properties, algorithms can accurately predict optimal lipid-to-surfactant ratios, target particle sizes, and encapsulation efficiencies [29]. This digital transformation will replace classical empirical

trial-and-error optimization, compressing developmental timelines and reducing preclinical costs. Finally, the standardization of continuous microfluidic manufacturing technologies will ensure absolute homogeneity in particle sizes across commercial-scale production batches.

CONCLUSION

The application of nanocarrier architectures represents a highly sophisticated and scientifically validated paradigm for overcoming the systemic delivery barriers governing poorly water-soluble drugs. By exploiting the physical principles of nanoscale curvature, nanocarriers drastically elevate saturation solubility and accelerate dissolution velocity, effectively neutralizing the biopharmaceutical challenges associated with BCS Class II and Class IV active ingredients. Beyond simple physical dissolution, these systems provide precise cellular transport pathways, utilizing transcellular endocytosis and recruitment of the intestinal lymphatic system to optimize systemic bioavailability while bypassing damaging hepatic first-pass metabolism.

However, widespread clinical translation requires solving fundamental technical limitations regarding low drug mass loading, long-term thermodynamic stability, and the scaling constraints of batch manufacturing methods. Future progress must combine AI-driven computational formulation discovery with microfluidic assembly lines to establish standardized, robust production protocols. In conclusion, while translation barriers remain, the targeted modification of nanomedicines offers an indispensable framework for unlocking the therapeutic potential of the next generation of insoluble pharmaceuticals.

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