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Review Article

Lipid Nanoparticles for Oral Delivery of Poorly Water-Soluble Drug

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ABSTRACT

The oral route remains the preferred method for drug administration; however, a significant proportion of new chemical entities exhibit poor aqueous solubility (BCS Class II and IV), leading to low and inconsistent bioavailability.This review aims to evaluate the current landscape of lipid nanoparticle (LNP) technologies, specifically Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs), as strategies to enhance the oral absorption of hydrophobic drugs. It synthesizes technical formulation parameters, absorption mechanisms, and translational barriers.The review examines formulation strategies, physicochemical characterization, and in vivo performance across various drug classes.lipid-based nanocarriers demonstrate 2- to 155-fold improvements in oral bioavailability by enhancing drug solubilization, protecting against gastrointestinal degradation, and facilitating intestinal lymphatic transport to bypass hepatic first-pass metabolism. Advanced NLC formulations offer superior drug loading and stability compared to first-generation SLNs. While LNPs present a robust platform for overcoming oral delivery barriers, challenges such as long-term storage stability, industrial scalability, and the need for more clinical validation remain. Future directions include the integration of 3D printing and hybrid lipid-polymer systems to further optimize delivery outcomes.

INTRODUCTION

The pharmaceutical industry faces a persistent challenge where approximately 40% to 70% of new drug candidates are characterized by low aqueous solubility [1], [8]. These poorly water-soluble drugs, often categorized under the Biopharmaceutical Classification System (BCS) as Class II or Class IV, exhibit limited dissolution in the gastrointestinal (GI) fluids, resulting in poor oral bioavailability and suboptimal therapeutic effects [13], [19]. To address these hurdles, nanotechnology-based delivery systems have emerged as a revolutionary approach [9], [10].

Lipid nanoparticles (LNPs) have garnered significant attention due to their ability to encapsulate lipophilic drugs within a biocompatible and biodegradable lipid

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matrix [6], [12]. Unlike traditional formulations, LNPs provide a multifaceted solution: they increase the effective surface area for drug dissolution, protect sensitive molecules from the acidic and enzymatic environment of the stomach, and utilize specialized physiological pathways for absorption [15], [21]. This review provides a comprehensive analysis of the evolution, formulation strategies, and translational potential of lipid nanoparticles in oral drug delivery, drawing on findings from a wide-ranging corpus of research [3], [11],

2. Evolution of Lipid Nanoparticle Systems

The development of lipid-based carriers has progressed through several generations, each designed to overcome the limitations of its predecessor.

2.1. First-Generation: Solid Lipid Nanoparticles (SLNs)

Solid Lipid Nanoparticles (SLNs) were developed in the early 1990s as an alternative to emulsions and liposomes. They are composed of lipids that remain solid at both room and body temperatures, such as triglycerides, fatty acids, or waxes [1], [15]. SLNs offer several advantages, including the avoidance of organic solvents in many preparation methods, high biocompatibility, and the ability to provide controlled drug release [35], [39]. However, the highly crystalline nature of the solid lipid matrix can lead to a limited drug loading capacity and the potential for drug expulsion during storage as the lipid undergoes polymorphic transitions into a more ordered crystal lattice [7], [12].

2.2. Second-Generation: Nanostructured Lipid Carriers (NLCs)

To address the stability and loading issues associated with SLNs, Nanostructured Lipid Carriers (NLCs) were introduced. NLCs consist of a blend of solid lipids and liquid lipids (oils), which creates an imperfect or "disorganized" lipid matrix [2], [4]. This less-ordered structure provides more space for drug molecules, leading to significantly higher encapsulation efficiency and reduced drug leakage [17], [36]. NLCs are formulated from physiological lipids that are generally recognized as safe (GRAS), facilitating their path toward clinical application [4], [12].

2.3. Emerging Platforms: LCNPs and Hybrid Nanoparticles

Recent research has expanded into more complex systems such as Lipid-Based Liquid Crystalline Nanoparticles (LCNPs), which utilize lipids like soy phosphatidylcholine and glycerol dioleate to form unique internal structures that further enhance drug solubility and permeability [23], [30]. Additionally, Solid Lipid-Polymer Hybrid Nanoparticles (SLPNs) combine the high loading and stability of polymers with the biocompatibility of lipids, offering a synergistic approach for the delivery of lipophilic bioactive compounds [10], [29], Other variations include self-emulsifying drug delivery systems (SEDDS) and self-nanoemulsifying systems (SNEDDS), which spontaneously form fine oil-in-water emulsions in the GI tract [6],

3. Technical Formulation Strategies

The performance of LNPs is intrinsically linked to the meticulous selection and ratio of their components.

3.1. Selection of Lipid Matrices

The choice of lipid depends on the drug's solubility in the lipid melt and the desired release profile. Common solid lipids include Compritol 888 ATO (glyceryl behenate), Precirol ATO 5 (glyceryl palmitostearate), stearic acid, and Dynasan-114 [18], [19], [21]. In NLC formulations, liquid lipids such as oleic acid, Labrafac PG are incorporated to disrupt the crystalline structure [2], [18], [26]. The ratio of solid to liquid lipid typically ranges from 70:30 to 99.9:0.1, depending on the specific formulation goals [7].

3.2. Surfactant Systems and Stabilization

Surfactants are critical for reducing the interfacial tension and preventing particle aggregation. Commonly used stabilizers include Poloxamer 188, Tween 80, lecithin, and sodium cholate [5], [14], [19]. The HLB (hydrophilic-lipophilic balance) value of the surfactant system is often matched to the lipid matrix to ensure optimal stability [15]. For instance, a combination of sorbitan trioleate and polysorbate 80 in a 10:90 ratio has been used effectively [15], and some formulations utilize auxiliary agents like polyvinylpyrrolidone

(PVP) as cosurfactants to further stabilize the nanoparticles [14].

3.3. Advanced Formulation Parameters

Technical data reveals that particle size and zeta potential are the primary determinants of LNP performance. Particle sizes for SLNs and NLCs generally fall within the range of 50 nm to 1000 nm, with smaller particles (around 100-200 nm) being less susceptible to blood clearance and more effective at mucosal adhesion [7], [11], [21]. Zeta potential values, which represent the surface charge, are ideally above +30 mV or below -30 mV to ensure electrostatic stabilization [21], [22]. For example, loperamide-loaded SLNs have shown zeta potentials ranging from -47.33 mV to -54.63 mV [5], while paclitaxel-loaded SLNs achieved a positive charge of +39.1 mV using stearylamine [22]. Cryoprotectants such as mannitol, glucose, or trehalose are often added before freeze-drying to maintain the integrity of the nanoparticles during storage [7], [21].

4. Manufacturing and Preparation Methodologies

The scalability of LNPs is one of their most attractive features. High-Pressure Homogenization (HPH) is the gold standard for industrial production, as it is a solvent-free process that can be conducted in both hot and cold modes [2], [15], [21]. Hot homogenization involves melting the lipid and dispersing it in a hot surfactant solution, while cold homogenization uses high-pressure milling of solid lipid-drug mixtures [7].

Other laboratory-scale methods include:

Solvent Emulsification-Evaporation: This technique involves dissolving the drug and lipid in an organic solvent, which is then emulsified in an aqueous phase; the solvent is subsequently evaporated to form nanoparticles [5], [14], [16].

Microemulsion-Based Synthesis: This method involves the formation of a warm microemulsion that is subsequently dispersed into cold water, causing immediate precipitation of the lipid nanoparticles [7], [21].

Modified Solvent Injection and Diffusion: These methods rely on the rapid diffusion of a water-miscible solvent from the lipid phase into the aqueous phase, leading to the formation of fine particles [21], [22].

Microfluidics: Although less common, microfluidics and microfluidizer technologies are gaining traction for their ability to produce highly monodisperse nanoparticles with precise control over size and drug distribution [23], [31].

4. Mechanisms of Bioavailability Enhancement

The multi-fold increase in bioavailability observed with LNPs is the result of several synergistic physiological mechanisms.

4.1. Solubilization and Dissolution Kinetics

By reducing the drug particles to the nanometer scale, LNPs significantly increase the surface area available for interaction with the GI fluids. This leads to an increased dissolution rate and the formation of a micellar solution, which facilitates the transport of the drug to the absorption site [3], [15]. LNPs have been shown to overcome the dissolution limitations of BCS Class II and IV drugs by ensuring that the drug remains in a solubilized state throughout its transit in the GIT [8], [13].

4.2. Gastrointestinal Protection and Residence Time

The solid lipid matrix acts as a physical barrier, protecting encapsulated drugs from the harsh acidic environment of the stomach and the enzymatic degradation (e.g., by proteases or lipases) in the intestine [1], [6], [13]. Furthermore, the small size and adhesive properties of lipid-based nanocarriers allow them to adhere to the GI mucosa or enter the intervillar spaces, thereby increasing the residence time and providing a longer window for absorption [15].

4.3. Intestinal Lymphatic Transport and P-gp Inhibition

One of the most powerful advantages of LNPs is their ability to stimulate intestinal lymphatic transport. Highly lipophilic drugs (log $P > 5$) encapsulated in lipid nanoparticles can be taken up by M-cells in the Peyer's patches or absorbed via enterocytes into the chylomicron pathway [6], [11], [20]. This allows the drug to enter the systemic circulation through the thoracic duct, effectively bypassing the portal vein and hepatic first-pass metabolism [18], [25]. Additionally, many surfactants used in LNPs, such as Tween 80 and sodium cholate, can inhibit P-glycoprotein (P-gp) efflux pumps,

thereby increasing the net absorption of drugs that are substrates for these transporters [3], [5], [12], [26].

5. Quantitative Bioavailability Outcomes: Case Studies

The literature provides extensive evidence of the efficacy of LNPs across various therapeutic categories.

Oncology: Paclitaxel-loaded SLNs demonstrated a 10-fold increase in plasma exposure compared to free drug solutions [22]. Similarly, curcumin-loaded SLNs achieved bioavailability improvements of up to 155-fold, demonstrating the potential for delivering natural bioactive compounds [21].

Cardiovascular Health: Simvastatin formulations using NLCs achieved an 8.99-fold higher absorption than the plain drug [18]. Other studies have reported multi-fold improvements for apixaban, rosuvastatin, and olmesartan [19].

Neurology and Psychiatry: Apomorphine-loaded SLNs showed 12- to 13-fold higher bioavailability than traditional solutions [21].

Gastrointestinal Disorders: Loperamide-loaded SLNs increased the relative bioavailability by 153% to 227% compared to marketed tablets [5].

Anti-infectives: LNPs have significantly enhanced the bioavailability of drugs like tilmicosin, efavirenz, and lamivudine [7], [15].

6. Translational Insights and Industrial Barriers

Despite the overwhelming evidence of efficacy in preclinical models, several hurdles must be cleared for wide-scale commercialization.

6.1. Scalability and Regulatory Considerations

The use of High-Pressure Homogenization and other solvent-free methods makes the industrial scale-up of LNPs feasible [2], [15]. However, maintaining consistent particle size and drug loading across large batches is a complex engineering challenge [19], [27]. Furthermore, while most lipids used are GRAS, the regulatory approval of the final nanoparticle product requires extensive toxicity and safety studies, particularly if high concentrations of surfactants are used [17], [21]. Currently, few LNP-based oral products have reached the market, such as Mucosolvan retard capsules, but more are in clinical trials [4], [15], [28].

6.2. Physical Stability and Storage Challenges

A major technical barrier is the physical stability of SLNs. Over time, the solid lipids can undergo polymorphic transitions (e.g., from the α or β' form to the more stable β form), which reduces the space available for drug molecules and can lead to drug expulsion [12], [21]. Additionally, particle aggregation and gelation are risks during storage, particularly if the zeta potential is not sufficiently high to maintain repulsion [15], [24]. NLCs partially mitigate these issues by using liquid lipids to disrupt the crystalline lattice, but long-term stability remains a focus of ongoing research [26].

7. Research Gaps and Future Perspectives

The future of LNP technology lies in increased precision and personalization.

Advanced Manufacturing: 3D printing and microfluidic technologies offer the potential to create personalized dosage forms with exact drug loading and release profiles [23], [31].

Targeted Delivery: Functionalizing the surface of LNPs with ligands (e.g., for M-cells or specific receptors) could further enhance absorption and allow for site-specific delivery in the GIT [16], [30].

Artificial Intelligence: The integration of AI and machine learning for formulation optimization could accelerate the development of more stable and effective LNPs [8].

Clinical Validation: There is a critical need for more human clinical trials to bridge the translational gap from animal models to clinical practice [10], [28].

CONCLUSION

Lipid nanoparticles, encompassing SLNs, NLCs, and their hybrid variants, represent a transformative approach for the oral delivery of poorly water-soluble drugs. By utilizing biocompatible lipid matrices and innovative formulation strategies, these carriers effectively address the dual challenges of low solubility and high metabolism. The literature consistently demonstrates substantial, multi-fold improvements in bioavailability, supported by a deep understanding of

absorption mechanisms such as lymphatic transport and P-gp inhibition. While technical challenges related to stability and scalability persist, the continued evolution of lipid-based nanotechnology promises to redefine the standards of oral drug delivery in the coming decade.

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