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Lipid-based nanocarriers for oral drug delivery enhancement

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ABSTRACT

Oral drug delivery remains the most widely used form because of its non-invasive nature, and high patient compliance. The therapeutic efficacy of oral drugs is limited by lower aqueous solubility, low intestinal permeability, instability within the gastrointestinal (GI) tract, and extensive first-pass hepatic metabolism. These challenges are particularly significant for Biopharmaceutics Classification System (BCS) class II and IV drugs, as well as for biomacromolecules such as peptides and proteins, which are sensitive to enzymatic degradation and show minimal absorption. Consequently, achieving maximum bioavailability and consistent pharmacokinetic profiles through regular oral formulations remains a major challenge in pharmaceutical development.

Currently, various formulation, use particle size reduction, salt formation, and use of solubilizing particles, to improve oral drug delivery. However, these methods provide limited and inconsistent outcomes. Nanotechnology-based drug delivery systems, particularly lipid-based nanocarriers, are now majorly used because of their bioactivity, biodegradability, and are able to improve drug solubilization. Oral drug delivery has showed promise with lipid-based systems such liposomes, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLCs), self-emulsifying drug delivery systems(SEDDS), and ionizable lipid nanoparticles. This help improve the drug absorption through several mechanisms, including enhanced dissolution, protection from GI degradation, modulation of intestinal permeability, and lymphatic transport.

Limitations including formulation instability, scalability challenges, variability in in-vivo performance, and regulatory concerns related to safety and toxicity continue to restrict the clinical use of the nanocarriers. The aim of this review is to analyze the role of lipid-based nanocarriers in improving oral drug delivery, with focus on their classification, mechanisms, formulation strategies, and pharmaceutical applications.

KEY WORDS

Lipid nanoparticles; Liposomes; Drug development; Nanotechnology; Biopharmaceutics; Drug delivery systems

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Introduction

Oral drug delivery remains as widely accepted medication route in clinical practice due to its non-invasive nature with high patient compatibility, and cost-effectiveness. But the therapeutic efficacy of oral drugs is generally limited by poor bioavailability, which is a critical drawback of drug absorption. Bioavailability is influenced by several physicochemical and physiological factors, like drug solubility, permeability, stability within the GI tract [1]. Drugs under BCS class II and IV, show poor aqueous solubility and limited permeability, resulting in suboptimal therapeutic outcomes. The oral delivery of biomacromolecules such as peptides and proteins possess additional challenges due to their susceptibility to enzymatic degradation, high molecular weight, and poor membrane permeability. These collectively restrict the availability of therapeutically important compounds required for the development of advanced drug delivery strategy [2].

Approximately 70% of newly developed drugs show poor aqueous solubility, which directly affects their dissolution rate and absorption in the GI tract. The oral delivery of therapeutics, including nucleic acids and peptide-based drugs, remains a significant challenge due to rapid degradation and limited permeability. These challenges present the requirement for innovative drug delivery platforms capable of overcoming both physicochemical and biological barriers [3].

Nanotechnology-based drug delivery systems have appeared as promising research associated with oral formulations [4]. Within these, lipid-based nanocarriers have gained traction because of their physicochemical characteristics and low immunogenicity. These systems use naturally occurring or synthetic lipids to encapsulate therapeutic agents, hence improving their solubility, stability, and absorption. Lipid-based nanocarriers contain liposomes, SLNs, NLCs, SEDDS, and ionizable lipid nanoparticles (LNPs) [5]. The ability of lipid-based nanocarriers to increase the oral bioavailability is due to multiple mechanisms which include enhanced drug solubilization in the gastrointestinal milieu, protection of labile drugs from enzymatic degradation, modulation of intestinal permeability, and facilitation of lymphatic transport. Also, the lipid-based systems have the capability of delivering a broad range of therapeutic agents, involving hydrophobic drugs, peptides, proteins, and nucleic acids [6].

Lipid-based nanocarriers for medication delivery have been the subject of extensive research. Zhao et al., studied the advantages of lipid-based systems over polymeric and metallic nanocarriers, emphasizing their superior biocompatibility, reduced toxicity, and enhanced therapeutic efficacy [7]. The study also described various types of lipid-based nanocarriers, including traditional liposomes and advanced systems like as ionizable lipid nanoparticles, which have been successfully utilized for nucleic acid delivery and vaccine development.

Mandal et al., discussed the character of lipid-based nanocarriers in increasing the oral delivery of poorly soluble drugs, particularly focusing on SLNs, NLCs, and SEDDS [8]. These systems were studied to increase the drug solubility, protect drugs from GI degradation, and mediate lymphatic uptake. Similarly, Subramanian demonstrated that lipid-based nanocarriers improve intestinal absorption through solubilization, modulation of enterocyte transport mechanisms, and stimulation of lymphatic transport pathways [9].

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In peptide and protein delivery, Naim et al., presented the challenges associated with biomacromolecules and the potential of the lipid-based systems in protecting these molecules from enzymatic degradation and improving their permeability across the intestinal layers [10]. Dumont introduced advanced formulation strategies such as hydrophobic ion pairing (HIP), which enhanced the encapsulation efficiency of peptides in lipid nanocarriers, thereby improving their stability and delivery potential [11].

One of the primary challenges is the physical and chemical instability of these systems, which may result in drug leakage, aggregation, or degradation during storage. Also, large-scale manufacturing of lipid-based nanocarriers remains complex and cost-intensive, posing challenges for industrial translation. Rapid clearance by the reticuloendothelial system (RES), variability in in-vivo performance, and limited targeting efficiency also affects the therapeutic efficacy. Also, regulatory concerns related to safety, toxicity, and long-term effects of nanomaterials remain significant barriers to their clinical approval [12].

The primary aim of this review is to present an extensive analysis of lipid-based nanocarriers for enhancing oral medication delivery. The review aims to discuss the classification, action mechanism, formulation strategies, and pharmaceutical applications of the systems.

Classification of Lipid-Based Nanocarriers

Lipid-based nanocarriers are classified based on their structural organization, composition, and drug addiction mechanism.

Vesicular systems

The hydrophilic and lipophilic medications can be encapsulated in vesicular lipid-based nanocarriers, which are distinguished by lipid bilayers around an aqueous core. Among these, liposomes are extensively studied and clinically established structures. Hydrophilic medications can be incorporated into the aqueous compartment of liposomes, which are made up of one or more phospholipid bilayers concentrically organized around an aqueous core [5,10]. Lipophilic medications can be incorporated into the lipid bilayer. Their structural similarity to membranes helps in biocompatibility and reduces toxicity. Liposomes have recorded major clinical success, with formulations approved for cancer treatment, fungal infections, and other diseases. However, liposomes are associated with certain limitations which includes structural instability, drug leakage, and rapid clearance by the RES, which lowers their circulation time and therapeutic efficacy. Hence, surface modifications such as polyethylene glycol (PEGylation) have been introduced to enhance stability and improved systemic circulation. Niosomes are another class of vesicular systems that are structurally similar to liposomes but are composed of non-ionic surfactants instead of phospholipids [13]. These systems offer better chemical strength and cost-effectiveness linked to liposomes, while maintaining the capacity to encapsulate a variety of therapeutic agents.

SEDDS

Under GI fluids, SEDDS isotropic mixtures of oils, surfactants, and co-surfactants spontaneously create fine oil-in-water emulsions. The capacity of SEDDS to keep poorly water-soluble medications in a solubilized condition within the GI tract is their main benefit. As a result, medication absorption and bioavailability are enhanced [12].

Advanced and hybrid lipid-based systems

Current advancements in nanotechnology have led to the development of hybrid lipid-based nanocarriers. Lipid-polymer hybrid nanoparticles add the structural stability of polymeric systems with lipid biocompatibility, resulting in improved drug loading, controlled release, and enhanced stability. Biomimetic nanocarriers, such as cell membrane-coated nanoparticles, are designed to escape the immune system and improve targeting efficiency. Stimuli-responsive lipid-based nanocarriers present another emerging class, where drug release is triggered by specific physiological conditions such as pH, temperature, or enzymatic activity [14].

Ionizable lipid nanoparticles

Ionizable LNPs present a highly advanced class of lipid-based nanocarriers designed for the delivery of nucleic acids, including small interfering RNA (siRNA) and messenger RNA (mRNA). These systems use ionizable lipids that remain neutral at physiological pH but become positively charged in acidic environments, causing endosomal escape and intracellular free of the encapsulated nucleic acids. The advantages of LNPs include high encapsulation efficiency, reduced toxicity and the potential to deliver a variety range of nucleic acid therapeutics [15].

Oral Drug Delivery Enhancement

Solubility and dissolution

Lipid-based nanocarriers attaches drugs into lipid matrices, thus maintaining them in a solubilized state within the gastrointestinal environment. Lipid-based formulations that come into contact with GI fluids, such SEDDS and lipid nanoparticles, aid in the creation of tiny emulsions. These systems promote the solubilization of poorly water-soluble drugs in the intestinal milieu and prevent precipitation, thus improving their absorption. This mechanism is important for BCS class II drugs [16].

Protection from GI degradation

The gastrointestinal tract presents a hostile environment for drug molecules, characterized by acidic pH in the stomach and various digestive enzymes such as pepsin, trypsin, and chymotrypsin. These conditions can degrade sensitive drugs, like peptides and proteins, resulting in reduced therapeutic efficacy. Lipid-based nanocarriers provide a protective barrier by encapsulating the drug within lipid layers, shielding it from exposure to GI conditions. This protective effect is critical for biomacromolecules, which are highly susceptible to enzymatic degradation and structural denaturation [17].

Facilitation of lymphatic transport

Lipid-based systems can facilitate the intestinal lymphatic system's transport of lipophilic medications, in contrast to conventional drug absorption, which takes place via the portal vein. After digestion, lipids are incorporated into chylomicrons within enterocytes and transported through the lymphatic circulation. Drugs with lipid-based nanocarriers can be co-transported along this pathway, thus bypassing hepatic metabolism and directly entering systemic circulation. This mechanism significantly enhances the bioavailability of drugs. Lymphatic transport is advantageous for highly lipophilic drugs and plays a major role in improving their therapeutic efficacy [18].

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Modulation of intestinal permeability

Lipid-based nanocarriers interact with biological membranes and modulate membrane fluidity, thereby helping drug transport across the epithelial barrier. Lipids and surfactants present in these formulations alter the integrity of tight junctions, causing paracellular transport. Also, lipid-based systems enhance transcellular transport by promoting the partitioning of lipophilic drugs into the cell membrane. These interactions improve the permeability of drugs [19].

Cellular uptake and endocytic pathways

Lipid-based nanocarriers can be absorbed by intestinal epithelial cells via various endocytic pathways, including clathrin-mediated endocytosis, caveolae-mediated uptake, and macropinocytosis. Specialized cells such as microfold cells located in Peyer's patches promote the transport of nanoparticles over the intestinal barrier [20].

Controlled drug release

The lipid matrix can be modified to regulate the release rate of the encapsulated drug, thus maintaining therapeutic plasma concentrations over a certain period. Controlled release improves drug efficacy and reduces dosing frequency and fluctuations in drug levels [21].

Formulation and Characterization

Preparation techniques

The preparation of lipid-based nanocarriers involves various techniques performed to achieve nanoscale particle size, uniform distribution, and high drug encapsulation efficiency. Among these, high-pressure homogenization is one of the widely used methods to produce SLNs and NLCs [18]. This technique uses high mechanical forces to reduce particle size, resulting in stable nanosuspensions. Emulsification techniques are also used in the formulation of lipid nanocarriers. In this method, lipids are dispersed in an aqueous phase with the help of surfactants to form oil-in-water emulsions. Subsequent cooling or solvent evaporation leads to the formation of nanoparticles. The microemulsion method involves the formation of thermodynamically stable systems composed of lipids, surfactants, and co-surfactants. These systems form nano-sized droplets under controlled conditions, which upon dilution or cooling result in the formation of lipid nanoparticles with narrow size distribution. Self-assembly is another technique, in the formulation of SEDDS. In this process, lipids and surfactants spontaneously organize into nanostructures upon contact with gastrointestinal fluids [22].

Factors affecting formulation

The performance of lipid nanocarriers is influenced by formulation parameters. The type of lipid used determines the structural integrity, drug loading capacity, and release profile of the system. Surfactant concentration plays an important role in stabilizing nanoparticles by reducing interfacial tension and preventing aggregation. Particle size is another critical factor, as smaller particles provide a larger surface area, improving dissolution, cellular uptake, and overall bioavailability [23-25].

In Vitro and In Vivo characterization

Characterization of lipid nanocarriers is essential to evaluate their physicochemical characteristics and predict their biological performance. Physicochemical characterization includes the determination of particle size and polydispersity index (PDI), which influences drug release and absorption. Zeta potential is studied to estimate the surface charge and colloidal stability, while morphological analysis using transmission electron microscopy (TEM) or scanning electron microscopy (SEM) provides insights into particle shape and structural integrity. Encapsulation efficiency is measured to determine the proportion of drug successfully incorporated within the carrier system [20].

In vitro studies are conducted to assess drug release kinetics and stability under simulated physiological conditions. These studies provide valuable information regarding the release profile and shelf stability of the formulation. Biological evaluation is performed using intestinal cell models such as Caco-2 cells, which simulate the human intestinal epithelium and are used to study drug permeability [26].

In vivo evaluation involves pharmacokinetic and bioavailability studies to determine the absorption, distribution, and systemic exposure of the drug. These are important for confirming the efficiency of lipid-based nanocarriers in improving oral drug deliver y [27].

Pharmaceutical Applications

Peptide and protein drug delivery

Encapsulation of peptides and proteins within lipid matrices provides protection against enzymatic degradation and harsh acidic conditions, thus preserving their structural integrity. Also, lipid-based systems improve permeability by facilitating interaction with intestinal membranes and promoting transcellular transport. Major achievement is the HIP strategy, which involves the formation of a structure between a charged peptide and an oppositely charged amphiphilic molecule. This process increases the lipophilicity of the peptide, ensuring its addition into lipid-based nanocarriers [28,29].

Cancer therapy

Lipid-based nanocarriers have been explored for cancer therapy due to their capacity to increase drug targeting and reduce systemic toxicity. These systems facilitate the delivery of chemotherapeutic agents to tumor tissues via enhanced permeability and retention (EPR) effect, allowing for selective accumulation at the tumor site. Also, lipid-based carriers can be engineered for controlled drug release, therefore maintaining therapeutic drug concentrations and minimizing adverse effects [30].

Nutraceutical delivery

Lipid-based nanocarriers play an important role in improving the delivery of nutraceuticals such as vitamins, polyphenols, and carotenoids which can be attached into lipid matrices, improving their stability and absorption in the GI tract [31]. These protect nutraceuticals from degradation and promote their transport across intestinal barriers.

CNS and chronic diseases

Lipid-based nanocarriers offer a promising approach to improve drug delivery by improving absorption and enabling targeted delivery. Their ability to modulate drug release and increase bioactivity promotes improved therapeutic outcomes. Also, lipid-based systems can drive the delivery of drugs with poor permeability, thereby increasing their effectiveness [32-34].

Challenges and Limitations

Stability issues

These are prone to aggregation, polymorphic transitions of lipids, and drug expulsion during storage, particularly in SLNs due to

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lipid crystallization. Also, oxidative degradation of lipids affects the integrity of the formulation and reduce drug efficacy. Variations in temperature and pH during storage and administration further affects the stability and performance of the nanocarriers [35].

Scale-Up challenges

Techniques such as high-pressure homogenization and emulsification require specialized equipment and precise control over parameters, which increases production costs. During large-scale production, it is still difficult to maintain uniformity between batches in particle size, drug loading, and stability [36,37].

Biological barriers

Macrophages in the liver and spleen recognize and eliminate nanoparticles, reducing their circulation time and therapeutic efficacy. Also, interactions with plasma proteins lead to opsonization and subsequent uptake by phagocytic cells. Variability in gastrointestinal conditions and enzymatic activity also influences the absorption and bioavailability of lipid-based formulations [38].

Regulatory issues

The deficiency of standardized guidelines for the estimation of nanomedicines expands the approval process. Concerns related to toxicity, immunogenicity, and long-term safety require extensive preclinical and clinical studies. Also, the complexity of these systems poses difficulties in characterization and quality control, which are required for regulatory approval [39].

Future Perspectives

Functionalized nanocarriers

Advanced functionalization strategies are being developed to improve the targeting and efficiency of lipid-based nanocarriers. Surface modification with ligands, antibodies, or peptides ensures site-specific drug delivery, thus improving therapeutic efficacy and minimizing off-target effects. Stimuli-responsive systems that allows to leave drugs in response to specific physiological triggers, such as pH, temperature, or enzymatic activity, are also under research [28].

Personalized medicine

The addition of lipid-based nanocarriers with personalized medicine shows a major increment in pharmaceutical sciences. Drug delivery systems depend on individual patient characteristics, such as genetic profile and disease state, can improve therapeutic outcomes and reduce adverse effects. Lipid nanocarriers offer the flexibility to design customized formulations that meet patient-specific requirements [29].

Clinical translation

The success of lipid-based nanocarriers in formulations, including liposomal drugs and lipid nanoparticle-based therapeutics, highlights their capability. Continued research focusing on improving formulation strategies, stability, and conducting clinical trials will be essential for expanding their use [31].

Sustainable nanotechnology

The use of biocompatible and biodegradable lipids derived from natural sources can reduce environmental impact and improve safety profiles. Also, the development of cost-effective and scalable manufacturing processes will help the widespread usage of lipid-based nanocarriers [40].

Conclusion

Lipid-based nanocarriers have emerged as an effective platform for improving oral drug delivery, addressing critical challenges linked with poor solubility, limited permeability, and instability of therapeutic agents. Their physicochemical properties, including biocompatibility, biodegradability, and ability to a wide range of drugs, contribute to pharmacokinetic and pharmacodynamic profiles. Through mechanisms such as enhanced solubilization, protection from GI degradation, lymphatic transport, and controlled drug release, these systems improve oral bioavailability and therapeutic efficacy. However, challenges related to stability, large-scale manufacturing, biological barriers, and regulatory approval must be studied to ensure their successful translation into clinical practice. Future research should focus on the development of advanced functional nanocarriers, integration with personalized medicine, and the establishment of sustainable and scalable production methods. With continued research, lipid-based nanocarriers are expected to drives a major role in the growth of oral drug delivery systems.

Disclosure Statement

No potential conflict of interest was reported by the author.

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