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Lipid-based Nanoparticles as Oral Drug Delivery Platforms for Overcoming Gastrointestinal Absorption Barriers and Enhancing the Bioavailability of Peptide- and Protein-based Therapeutics

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ABSTRACT

The oral delivery and formulation of therapeutic peptide- and protein-based biopharmaceuticals continue to pose significant challenges within the pharmaceutical domain. These biomolecules exhibit inherently low oral bioavailability, primarily due to limited gastrointestinal solubility and permeability. Contributing factors include high molecular weight, poor membrane permeability, and extensive degradation by chemical and enzymatic processes within the gastrointestinal tract, all of which restrict their therapeutic potential. This review critically examines the barriers associated with oral administration of peptide/protein therapeutics and emphasizes the emerging role of lipid-based drug delivery systems (LBDDSs) specifically, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) as innovative platforms to overcome these limitations. These lipid-based systems offer several pharmacokinetic and pharmacodynamic advantages, including protection against enzymatic degradation, improved drug solubility and absorption, enhanced mucosal permeability, reduced first-pass metabolism, and the potential for controlled and sustained release. The nanoscale size and modifiable surface properties of SLNs and NLCs further facilitate targeted delivery, prolonged systemic circulation, and improved therapeutic index. LBDDSs are characterized by favorable features such as ease of fabrication, scalability, biodegradability, biocompatibility, low systemic toxicity, and the ability to encapsulate both hydrophilic and lipophilic agents. These attributes collectively underscore their promise in enhancing oral bioavailability and therapeutic efficacy of peptide/protein-based drugs. Despite these advantages, critical formulation challenges particularly those related to plasma stability, membrane translocation, and circulation half-life persist and require further investigation in future drug development efforts.

INTRODUCTION

In recent decades, escalating demands for cost-effective healthcare, alongside the need for therapeutics with superior efficacy and safety profiles, have driven the pharmaceutical industry to prioritize the development of biotechnological agents, particularly peptide- and protein-based drugs (1). Unlike conventional small-molecule active pharmaceutical ingredients (APIs), these biopharmaceuticals demonstrate enhanced therapeutic outcomes due to their elevated potency, target selectivity, and specificity for extracellular receptors (2). Peptides and proteins, being endogenous biomolecules, serve a wide range of physiological functions including roles as hormones, enzyme regulators, antibiotics, signaling mediators, and structural components. Given their functional versatility, even minor structural abnormalities, such as mutations in amino acid sequences, can result in severe pathological conditions including diabetes (3), growth hormone deficiencies such as dwarfism (4), cystic fibrosis (5), thalassemia (6), or coagulation disorders (7,8). Owing to their biological specificity and high binding affinity, peptide- and protein-based molecules have been increasingly employed in the treatment of these and other disorders (9,10).

Protein stability is governed by a dynamic equilibrium among several molecular forces, including electrostatic interactions, hydrogen bonding, van der Waals forces, and hydrophobic effects. These interactions collectively stabilize the secondary, tertiary, and quaternary

structures of proteins. Disruption of this balance can induce conformational destabilization, leading to denaturation and loss of function (11,12). Additionally, the chemical and physical stability of protein-based therapeutics is highly sensitive to environmental factors such as pH, ionic strength, temperature, shear forces, non-aqueous solvents, pressure, metal ions, detergents, and adsorption all of which may be encountered during formulation, sterilization, and lyophilization. These stressors may result in protein aggregation, precipitation, immunogenicity, and bio-inactivation (13–15). Despite these challenges, peptide- and protein-based therapeutics offer several advantages, including biocompatibility, customizable in vivo activity, chemical diversity, and specific tissue targeting. Modern synthetic approaches most notably solid-phase peptide synthesis (e.g., Merrifield's method) enable precise design and sequence incorporation at the molecular level (16). Nonetheless, the inherent physicochemical limitations of protein drug candidates remain formidable obstacles for formulation scientists and pharmaceutical manufacturers.

Historically, peptides were not regarded as viable drug candidates, largely due to issues such as susceptibility to proteolytic degradation, metabolic instability, short biological half-life, complex synthesis processes, and elevated production costs (17). These factors, particularly in the context of parenteral administration, have undermined patient compliance and cost-efficiency, especially considering the low oral bioavailability of most peptides (typically <10%) (18). However, peptides also possess distinct pharmacological benefits, including rapid biodegradation into non-toxic metabolites (2), minimal drug-drug interaction potential, low immunogenicity, enhanced tissue penetration due to their small size, and high potency per unit mass. Regulatory approval rates for peptide-based therapies exceed 20%, which is approximately double that of conventional small-molecule drugs (17). Proteins, akin to peptides, have garnered increasing attention in pharmaceutical science, largely due to the advent of sophisticated analytical tools, molecular engineering techniques, and advancements in recombinant protein production. These innovations have facilitated the identification of endogenous proteins and peptides as therapeutic targets and contributed to the growth of protein-based biopharmaceuticals (19,20). Consequently, significant research has been directed toward developing scalable oral delivery systems capable of efficiently delivering protein/peptide drugs (21).

Nevertheless, oral administration of these macromolecules remains limited due to their poor bioavailability. Key barriers include enzymatic degradation (particularly in the gastrointestinal tract), large molecular size (22), poor stability in acidic environments (23), inadequate intestinal permeability, and rapid systemic clearance. Additionally, protein drugs often exhibit aggregation, adsorption to container surfaces, and immunogenic reactions, further complicating their formulation (24,25). Among these, proteolytic degradation and poor epithelial transport are the primary contributors to the low oral bioavailability of protein therapeutics often <1% although some novel formulations have reported increases to 30–50% (26,27). Due to their high molecular weight and hydrophilicity, protein-based drugs require specific epithelial transport mechanisms to enter systemic circulation. Without such mechanisms, their absorption via passive diffusion is negligible. Moreover, the acidic gastric environment and digestive enzymes exacerbate degradation, further impeding therapeutic efficacy (28). Currently, the intravenous (IV) route is the most commonly employed method for administering biopharmaceuticals. However, this mode of delivery is associated with poor patient compliance, unpredictable clearance kinetics (ranging from minutes to days), and potential risks related to systemic deposition and distribution. These limitations necessitate repeated high-dose administrations, thereby increasing the risk of adverse events (29,30).

Alternative parenteral routes, such as subcutaneous (SC) and intramuscular (IM) injections, are also utilized. Among these, SC injection is the most prevalent, particularly for vaccine delivery. Several factors including molecular weight, injection site, local physiological activity, and pathological conditions affect the absorption kinetics and bioavailability of protein therapeutics via the SC route (31). Proteins with molecular weights below 16,000 Da are primarily absorbed through local capillary diffusion, whereas larger proteins tend to enter systemic circulation via the lymphatic system. However, the latter pathway is associated with delayed absorption and higher susceptibility to enzymatic degradation during transit (31,32)

In recent years, considerable attention has been directed toward exploring non-invasive routes as alternatives to traditional parenteral administration methods for peptide and protein therapeutics. Investigated delivery pathways include nasal, ophthalmic, buccal, rectal, vaginal, transdermal, and pulmonary routes, each offering varying degrees of systemic absorption potential for macromolecular drugs such as peptides and proteins (28,33,40).

Among these, mucosal routes historically underutilized for systemic drug administration are increasingly recognized as promising alternatives, particularly for the delivery of high molecular weight and hydrophilic biotherapeutics (28,41). Mucosal surfaces such as those of the oral cavity, nasal passages, eyes, rectum, and vagina present several pharmacokinetic advantages over the gastrointestinal (GI) tract and dermal route. These include fewer physiological barriers, relatively rapid absorption, and avoidance of hepatic first-pass metabolism. However, despite these benefits, mucosal

delivery is limited by the challenge of formulating stable preparations suitable for localized, long-duration administration.

Oral administration remains the most preferred and widely accepted route for drug delivery, owing to its non-invasive nature, ease of self-administration, cost-effectiveness (due to non-sterile manufacturing), reduced risk of cross-infection, and high patient compliance, particularly for chronic disease management (42). Additionally, oral delivery avoids many of the complications associated with intravenous (IV) administration, such as catheter-related infections, drug extravasation, thrombosis, and procedural invasiveness.

Nevertheless, several physiological and biochemical barriers within the GI tract limit the effectiveness of oral administration for peptides and proteins. These barriers include enzymatic degradation in the lumen, acidic pH in the stomach, and poor permeability across the intestinal epithelial monolayer, all of which contribute to the overall low oral bioavailability of protein-based drugs (43).

Certain bioactive compounds are inherently unsuitable for oral administration due to their physicochemical characteristics (44). According to the Biopharmaceutics Classification System (BCS), a compound's oral bioavailability is primarily determined by its aqueous solubility and permeability across gastrointestinal epithelia (45). Many modern drug candidates, especially those identified through high-throughput screening, tend to exhibit high molecular weight and lipophilicity, complicating their oral absorption (46). Moreover, gastrointestinal instability and poor membrane permeability further hinder systemic availability. An additional limitation is the presence of efflux transporters such as P-glycoprotein, which actively pump many drugs out of enterocytes, reducing their intracellular concentration and systemic exposure (47). Irrespective of the administration route, the majority of peptide and protein therapeutics are unable to effectively reach their target tissues due to intrinsic limitations in their physicochemical profiles. This necessitates the use of specialized drug delivery and tissue-targeting strategies designed to enhance site-specific distribution and pharmacological activity. The aim of these delivery systems is to maximize the therapeutic concentration of the drug at the site of action while minimizing systemic exposure and off-target effects, thereby improving efficacy and reducing adverse reactions (48)

Peptide/Protein Drug Delivery

The emergence of novel biotechnological therapeutics, advancements in chemical synthesis, and the application of recombinant DNA technology have collectively positioned protein and peptide-based drug development as a pivotal domain in pharmaceutical research. These advancements have facilitated the production of numerous large-scale therapeutic agents including monoclonal antibodies, hormones, and vaccines. According to PhRMA reports from 2018 and 2019, there were approximately 4,751 and 5,422 biotechnological drug candidates, respectively, undergoing research and development for over 100 disease categories, such as cancer, infectious diseases, autoimmune disorders, HIV/AIDS, and parasitic infections. These candidates were either in human clinical trials or under FDA review (49). Despite these developments, significant challenges remain in achieving efficient delivery of peptide/protein-based drugs, particularly via the gastrointestinal (GI) tract (50), and across the blood-brain barrier (BBB) in the treatment of central nervous system disorders. In recent decades, an increasing number of protein-based therapeutics have entered both preclinical and clinical trial phases, with over 400 recombinant peptides/proteins developed and more than 1,300 undergoing clinical evaluation (51). Their relatively large molecular size enables interaction with binding sites not accessible to small molecule drugs, including targets within intracellular protein-protein interaction networks known to be dysregulated in various diseases. Although these drugs can target such intracellular domains, many are primarily directed at extracellular sites and are administered parenterally, thereby circumventing cellular penetration, unlike mucosal delivery mechanisms. A primary barrier to effective oral administration of peptide/protein drugs lies in the ability to traverse both intestinal epithelial membranes and the membranes of target cells. To design effective oral delivery systems for biopharmaceuticals, a comprehensive understanding of the transport mechanisms involved in GI absorption is essential. The key physicochemical attributes influencing these mechanisms include molecular weight, hydrophobicity or hydrophilicity, ionization state, and pH stability.

Transport Mechanisms in the Gastrointestinal Tract

Paracellular Transport: This route is characterized by the passage of molecules through aqueous pores within epithelial tight junctions, with dimensions varying across intestinal segments approximately 7–9 Å in the jejunum, 3–4 Å in the ileum, and 8–9 Å in the colon (75). The total absorptive surface area attributed to tight junctions is minimal, estimated at around 0.01% (52), thereby imposing strict limitations on the passage of solutes via this pathway. Despite such constraints, the paracellular route exhibits ionic selectivity, influenced by tissue-specific electrical resistance and collaboration with transcellular mechanisms. Factors such as ion concentration, charge selectivity, mole-fraction effects, and pH sensitivity influence permeability (53), while molecular properties such as lipophilicity and hydrogen bonding have negligible effects in this pathway.

Transcellular Transport: In this mechanism, molecules undergo endocytosis at the apical membrane and are subsequently released at the basolateral side. A notable example is glucose transport. The basolateral

membrane's low protein-lipid ratio results in a more permeable barrier than the apical side (54). The rate of transcellular transport is modulated by the molecule's size, hydrophobicity, surface charge, hydrogen bonding potential, ligand interactions, and the physiological environment of the GI tract. Two primary epithelial cell types mediate transport enterocytes (comprising about 99% of the epithelium) and M cells, which are predominantly located in Peyer's patches and follicle-associated epithelium (FAE) (55). M cells are especially adept at transcytosis of peptides, proteins, and nanoparticles to local lymphoid tissues, rendering them targets for oral biopharmaceutical delivery systems (56). These cells engage in various uptake processes including phagocytosis, clathrin-mediated endocytosis, and fluid-phase endocytosis (84). Though some studies report nanoparticle transit through intestinal villi, a consensus supports preferential uptake via the FAE and M cells. Nevertheless, the transcellular route is suboptimal for small lipophilic drugs, and its efficiency decreases notably in the colon compared to the paracellular pathway (57).

Carrier-Mediated Transport: This active, energy-dependent process facilitates the movement of specific molecules against their concentration gradient via membrane-bound transporters. Examples include β-lactam antibiotics, ACE inhibitors, monosaccharides, and amino acids. Studies using Caco-2 monolayers have shown that transferrin-receptor-mediated transport of conjugated insulin is significantly greater by 5 to 15-fold than through insulin receptors (58).

Receptor-Mediated Transport: This pathway involves ligand-specific receptor binding and subsequent internalization via mechanisms such as clathrin-mediated endocytosis, pinocytosis, and potocytosis (non-clathrin-mediated processes). Following receptor engagement, the ligand-receptor complex enters endosomes, where acidic conditions may promote dissociation and subsequent degradation. Upon internalization, peptides and proteins can access systemic circulation through two primary pathways: the hepatic portal vein and the intestinal lymphatics. Hydrophilic molecules predominantly enter the bloodstream via the portal vein, undergoing hepatic first-pass metabolism before systemic distribution. In contrast, lipophilic compounds, absorbed through the intestinal lymphatics, bypass hepatic metabolism and are transported directly to the systemic circulation via the vena cava.

Oral Drug Absorption

The effective absorption of orally administered drugs via the gastrointestinal (GI) tract is largely dependent on their aqueous solubility and membrane permeability. However, many pharmacological compounds exhibit poor aqueous solubility, which leads to reduced and variable bioavailability across individuals (59). In such cases, the co-administration of high-fat meals has been shown to significantly enhance oral bioavailability. This enhancement occurs through mechanisms such as delayed gastric emptying, stimulation of exocrine pancreatic secretions, inhibition of intestinal metabolism, lymphatic transport facilitation, increased intestinal permeability, reduced efflux by transporter proteins, and alterations in splanchnic blood flow (60). The emergence of lipid-based drug delivery systems (LBDDSs) in the 1990s addressed solubility issues associated with hydrophobic drugs by enabling the dissolution of these compounds within lipidic matrices, thereby promoting their dispersion and absorption across the intestinal epithelium. Upon enzymatic digestion of lipids in the intestinal lumen, monoacylglycerols and free fatty acids are generated, which contribute to the formation of mixed micelles. These micelles serve as vehicles for drug solubilization and facilitate their transport across the intestinal barrier. Following intestinal absorption, compounds may enter systemic circulation via two principal routes: the portal blood or lymphatic pathways. Most orally administered drugs are absorbed into the hepatic portal system, whereas highly lipophilic drugs (log P > 5) preferentially enter systemic circulation via intestinal lymphatics, thereby bypassing hepatic first-pass metabolism. This lymphatic uptake is particularly relevant for macromolecules and lipophilic compounds, given the enhanced permeability of lymphatic endothelium to nanoparticles. Moreover, the degree of lymphatic transport is influenced by the physicochemical properties of the dietary lipids present; long-chain triglycerides (C14–C18) are more effective than short-chain lipids in promoting lymphatic uptake (61).

Physiological Barriers to Peptide/Protein-Based Drug Absorption

Gastrointestinal Barriers: Advancements in molecular pharmacology have elucidated the intricate physiological and molecular mechanisms governing GI absorption, which are now being leveraged to design targeted oral delivery strategies for peptide- and protein-based biopharmaceuticals (62). Proteolytic degradation within the GI tract is a significant barrier to peptide drug absorption. This degradation is mediated by two main classes of enzymes: endopeptidases (e.g., trypsin, chymotrypsin, elastase), which cleave internal peptide bonds, and exopeptidases (e.g., aminopeptidase, carboxypeptidase A), which hydrolyze terminal residues. Proteolysis can occur throughout various compartments, including the intestinal lumen, brush border membrane, enterocyte cytosol, lysosomes, and other intracellular organelles (63). The gastric environment, characterized by the secretion of hydrochloric acid (HCl), potassium chloride (KCl), and sodium chloride (NaCl), maintains an acidic pH (1.5–3.5), which facilitates initial protein degradation into smaller peptides and amino acids via pepsin activation. However, this enzymatic activity is neutralized in the

duodenum due to the alkaline pH (~6.0), thereby terminating pepsin activity (64). The small intestine, particularly the duodenum and jejunum, is the principal site of peptide absorption due to high protease activity. Enzymes secreted by enterocytes at the brush border, along with pancreatic endo- and exopeptidases, further hydrolyze peptides. In contrast, regions such as the distal jejunum and ileum, which host Peyer's patches, exhibit reduced enzymatic activity (~20–30%) and may offer advantageous sites for targeted peptide delivery due to minimized enzymatic degradation (65).

Mucosal Barriers: The gastric and intestinal mucosa present additional challenges to the oral absorption of peptides. The stomach's mucosal barrier comprises three structural layers: a layer of tightly bound epithelial cells that prevents penetration of harmful substances; an insoluble mucus layer composed of mucins secreted by surface and neck cells; and a bicarbonate-rich fluid that buffers gastric acid. Additional components such as the glycocalyx, located atop gastric epithelial cells, are acidic and rich in sulfated mucopolysaccharides, which further hinder drug diffusion (66). Mucus secreted by goblet cells contains a matrix of mucin glycoproteins, enzymes, electrolytes, and water. The adhesive nature of mucin contributes primarily to the physical, rather than chemical, barrier function of the glycocalyx. The structural variation of mucus across the GI tract also influences drug permeability: the mucus is thicker in the stomach and colon and thinner in the small intestine, reflecting the functional specialization of each segment. Consequently, for a peptide or protein to be absorbed, it must first diffuse through both the mucus layer and glycocalyx before reaching the epithelial cell membranes, which constitute a highly viscous and selective barrier.

Nanomedicine: An Emerging Platform for Drug Delivery

Following drug administration, plasma drug concentration typically increases to a peak level, subsequently decreasing as the compound is metabolized and excreted. To maintain therapeutic efficacy, drug levels must remain within a defined "therapeutic window." This necessitates repeated dosing, with subtherapeutic or supratherapeutic levels leading to either treatment failure or systemic toxicity, respectively (67). Traditional formulations often lack the ability to sustain plasma levels within this therapeutic range, highlighting the need for advanced drug delivery systems. Nanomedicine, an interdisciplinary field integrating nanotechnology and pharmaceutical sciences, has emerged as a transformative approach to overcome the limitations of conventional drug delivery. It involves the use of nanostructured materials for the controlled, targeted, and sustained release of therapeutic agents (40). This approach is particularly advantageous for peptide/protein-based drugs, which suffer from poor oral bioavailability due to enzymatic degradation and limited permeability. Encapsulation of these drugs in nanocarriers not only enhances their stability and shelf life but also enables large-scale manufacturing of sterile oral dosage forms. Nanocarriers are typically engineered with specific physicochemical characteristics, such as particle size, surface charge, and release kinetics, to ensure site-specific delivery within the desired therapeutic range (68). These structures range from 1–100 nm in size and may encapsulate the drug in their core, disperse it in a matrix, or adsorb it onto the surface, thereby modulating systemic circulation time and mean residence time (MRT).

Lipid-based drug delivery systems (LBDDSs), in particular, have garnered attention due to their biocompatibility, high cellular penetration, intrinsic lipophilicity, and scalable manufacturing processes. Compared to polymeric and inorganic nanoparticles, lipid-based systems offer simpler fabrication and cost-effectiveness (69). These systems are categorized based on their formulation strategies and include:

Liposomes: These are spherical vesicles composed of one or more phospholipid bilayers enclosing an aqueous core. Liposomes vary in size (10–1000 nm) and represent the first generation of LBDDSs, primarily used for parenteral drug administration. Their advantages include low immunogenicity, high drug encapsulation efficiency, and sustained-release properties. However, challenges such as structural instability, rapid clearance by the reticuloendothelial system, and complexity in large-scale production persist. Surface modifications such as PEGylation and ligand conjugation have improved pharmacokinetics and therapeutic efficacy. Several liposome-based formulations have been clinically approved for diverse therapeutic applications. Examples include Doxil®, Myocet®, and Lipodox® for oncological indications; Ambisome® for fungal infections; Depocyt® for lymphomatous meningitis; DepoDur® for pain management; Epaxal® for hepatitis A immunization; and Inflexal® for influenza prophylaxis (32).

Lipoplexes: Lipoplexes are complex assemblies derived from liposomes, typically structured as multilamellar vesicles comprising positively charged lipid bilayers and negatively charged nucleic acids. These nanocarriers are formed via electrostatic self-assembly between cationic liposomes and nucleic acids, resulting in nanoscale scaffolds suitable for gene delivery applications. Due to their liposomal origin, lipoplexes inherit several physicochemical characteristics, including both their advantages and limitations. Notably, their transfection efficiency is often compromised due to the excessive binding of multiple cationic moieties to nucleic acids, which may hinder intracellular delivery and release mechanisms. Nonetheless, lipoplexes have shown promise in targeted delivery systems for neurological disorders and brain-related studies (70). Lipoproteins, naturally occurring lipid-based carriers in the human

body, exhibit structural and functional similarities to synthetic liposomes. Composed primarily of cholesterol, phospholipids, apolipoproteins, enzymes, and microRNAs, they naturally transport lipophilic molecules. Due to their endogenous origin, lipoproteins present high biocompatibility and reduced immunogenicity. These systems have been evaluated alongside other nanocarriers such as albumin and PEG-PLGA nanoparticles for their potential in treating central nervous system (CNS) disorders (144). Niosomes are vesicular systems characterized by a lamellar, self-assembled architecture consisting of non-ionic surfactants and cholesterol or its derivatives. These vesicles can encapsulate both hydrophilic and lipophilic agents and are advantageous over liposomes in terms of chemical stability, cost-effectiveness, and longer shelf-life (71).

Transferosomes: Transferosomes represent an advanced form of lipid-based vesicles. These are deformable liposomes formulated using phospholipids and edge activators (surfactants) to enhance membrane flexibility. Their composition allows superior transdermal and systemic delivery, and they share structural parallels with both liposomes and niosomes.

Solid Lipid Nanoparticles: Solid Lipid Nanoparticles (SLNs) are colloidal carriers with a solid lipid core matrix that remains solid at both room and body temperature (72).

Nanostructured Lipid Carriers: Nanostructured Lipid Carriers (NLCs) integrate a liquid lipid (oil) phase within a solid lipid matrix, resulting in a partially crystallized structure that enhances drug incorporation and storage stability.

Among the various lipid-based drug delivery systems (DDSs), SLNs and NLCs have emerged as leading platforms owing to their unique physicochemical properties and formulation versatility. SLNs, composed solely of solid lipids, offer controlled drug release due to restricted molecular mobility within the solid matrix. These have been developed into oral pellet forms, sustained-release capsules (e.g., Mucosolvan®), microparticles via spray drying, and nanopellets for oral administration (18,39,56).

Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLNs and NLCs are advanced lipid-based colloidal drug carriers engineered from biocompatible lipids (solid or liquid), surfactants, co-surfactants, and active pharmaceutical ingredients (APIs). SLNs are composed exclusively of solid lipids and surfactants, whereas NLCs include both solid and liquid lipids, offering greater drug-loading capacity and structural flexibility. Lipid excipients such as purified triglycerides, glyceride mixtures, and waxes ensure thermal stability at physiological conditions. Surfactants improve system stability, enhance cellular uptake, and increase bioavailability. Both systems combine the merits of traditional colloidal carriers (e.g., liposomes, polymeric nanoparticles) while minimizing their shortcomings. Key advantages include improved dissolution profiles, higher drug encapsulation efficiency, enhanced stability in physiological fluids, and the elimination of unpleasant taste in oral formulations. Furthermore, these systems exhibit reduced toxicity, avoidance of organic solvents, feasibility for industrial-scale production, and support for multiple administration routes including oral, parenteral, nasal, rectal, and ophthalmic. However, SLNs are not without limitations. These include relatively low drug loading capacity, the tendency for polymorphic transitions that may lead to drug expulsion during storage, and possible gelation under certain conditions (73). To overcome these challenges, NLCs were developed as second-generation lipid nanoparticles, offering enhanced loading capacity, improved stability, and reduced drug leakage. Several formulation techniques including high-pressure homogenization, solvent diffusion, and ultrasonication have been employed to optimize their physicochemical attributes (74). Efficient drug delivery via lipid nanoparticles necessitates rigorous characterization to ensure safety and performance. Critical parameters include particle size distribution, encapsulation efficiency, internal structure, surface morphology, degree of functionalization, and co-encapsulation potential. These characteristics directly influence the pharmacokinetics particularly the bioavailability, absorption profile, and tissue distribution of the loaded therapeutic agents. Thus, meticulous evaluation is essential for the successful clinical translation of SLNs and NLCs in drug delivery applications.

LBDDSs for Oral Delivery of Hydrophilic and Hydrophobic Peptide/Protein Therapeutics

Lipid-based drug delivery systems (LBDDSs) have demonstrated considerable potential in improving the oral bioavailability of hydrophobic peptide and protein-based therapeutics. While significant progress has been made in this area, the effective oral delivery of hydrophilic peptide-based drugs continues to face substantial challenges. To date, such approaches remain primarily within the realm of preclinical evaluation, with no commercially available pharmaceutical formulations (75). Several studies have examined the use of lipid-based carriers such as micelles, microemulsions, and nanocapsules for oral peptide delivery. For example, insulin a paradigmatic hydrophilic peptide has been encapsulated within various lipid nanostructures in both in situ and in vivo rodent models, demonstrating enhanced permeability, bioavailability, and pharmacodynamic efficacy (76,77). Notably, microemulsion-based delivery of SK&F 106760, a hydrophilic RGD peptide, resulted in a 50-fold improvement in systemic bioavailability following oral administration in vivo. Similarly, vasopressin-loaded microemulsions yielded increased bioavailability in situ,

and epidermal growth factor (EGF) microemulsions enhanced therapeutic outcomes in rat models of gastric ulceration. In another investigation, oral administration of β-lactamase via lipid-based systems yielded a 2.5-fold enhancement in bioavailability (224). Encapsulation of N-acetylglucosaminyl and N-acetylmuramyl dipeptides within lipid carriers showed a 10-fold increase in systemic exposure (78). Leuprolide acetate formulated in microemulsions demonstrated superior efficacy in vivo, while formulations of Hexarelin and DMP 728 both cyclic peptides exhibited 20-fold and 3-fold increases in intestinal permeability and bioavailability, respectively, in in situ models. In a canine model, DuP 532, an angiotensin II antagonist, delivered via microemulsion, showed a 3-fold enhancement in systemic bioavailability (79).

Furthermore, studies on calcitonin-loaded micelles and emulsions in rats and pigs demonstrated improved membrane transport and a four-fold increase in hypocalcemic response. Human growth hormone, when delivered in vivo in rabbits using a lipid-based system, achieved a 3.3% increase in systemic bioavailability. These findings underscore the potential of LBDDSs as a platform for advancing oral peptide/protein delivery through enhanced solubilization and protection from gastrointestinal degradation.

Regulatory Considerations, Commercialization Prospects, and Safety Assessment

Prior to market introduction, the regulatory status of excipients used in LBDDS formulations must be thoroughly evaluated in accordance with relevant regulatory authority requirements. However, the high financial burden associated with in vivo toxicological assessments often limits commercial interest, particularly in the case of polymer-based nanoparticles, which are underrepresented in marketed formulations. In contrast, lipid nanoparticles due to their reliance on excipients such as oils, surfactants, and stabilizers commonly used in food and cosmetic industries have seen broader application in oral and topical pharmaceutical products. Most excipients employed in LBDDS fabrication are biodegradable and biocompatible, with many classified as safe by regulatory agencies. Nonetheless, toxicity can occur at elevated concentrations. The U.S. Food and Drug Administration (FDA) provides detailed guidance through the Generally Recognized as Safe (GRAS) list and the Inactive Ingredient Guide (IIG), which delineate acceptable concentration ranges and approved uses for excipients across various administration routes. These references serve as critical tools for formulation scientists, offering data that supports the rational design of new LBDDSs by aligning excipient selection with safety and regulatory criteria. From a regulatory perspective, the translation of LBDDSs from bench to bedside demands robust preclinical and clinical validation of safety and therapeutic efficacy. Particular emphasis must be placed on immunogenicity and the stability of lipid-based excipients, which can vary under physiological conditions. Additionally, discrepancies between in vitro and in vivo findings often attributable to the complex environment of the gastrointestinal (GI) tract highlight the need for comprehensive studies to elucidate excipient-drug and excipient-tissue interactions (80). To address these translational gaps, a collaborative initiative involving academic and industry stakeholders the Lipid Formulation Classification System (LFCS) Consortium has been established (http://www.lfcsconsortium.org). This consortium aims to systematically evaluate dispersion and digestion behaviors of LBDDSs in vivo, which are critical parameters influencing therapeutic performance.

CONCLUSION

Nanotechnology offers promising strategies for enhancing oral bioavailability and therapeutic efficacy of a vast range of drugs; conventional chemical drugs with poor water solubility and biotechnological, peptide/protein-based drugs and biopharmaceuticals. Regarding the latter, their unique physicochemical and biopharmaceutical features pose challenge for their oral delivery. Hence, their success in site delivery highly depends on technologies and methods to modify these two features not influencing their biological function. In the recent decades numerous DDSs have been introduced and offered by nanotechnology to achieve as high successful delivery as possible and LBDDSs among all has been under investigation owing to their potential for oral delivery of hydrophilic, hydrophobic and lipophilic peptide- and protein-based drugs.

LBDDSs enhance solubility and bioavailability of drugs offering strategies such as gastrointestinal lymphatic transport, altering physiological and biochemical properties of gastrointestinal barriers, elevated solubilization and prolonged gastrointestinal retention. Although, such improvements rely on the encapsulation/loading rate and intrinsic composition of the material used during the fabrication process. Obviously, the choice of materials, such as excipients, will influence the success of delivery route which is determined both by lipid formulation design and peptide/protein molecule emphasizing that each. peptide/protein-loaded LBDDS must be designed uniquely. Such material must be in correlation with the drug of choice to achieve the maximum therapeutic efficacy and in-site dose.

Most of the scaffolds described in this review article suggest promising alternatives to overcome gastrointestinal enzymatic degradation and poor membrane penetration. Further systematic studies are required to evaluate their in-vivo efficacy in terms of peptide-/protein-based oral drug delivery. Besides “pharmaco-biotechnological” challenges mentioned in this review such as membrane permeability, protease

stability, delivery strategies and increased circulation half-life, there are inevitably several "industrial" challenges as well which finally hamper their industrial scale production and consequently their biomedical translation from lab to pharmaceutical market. "Oral bioavailability" still remains the main challenge of peptide/protein-based drug delivery. These factors could be addressed as materials cost, drug potential market feedback, regulatory status, simple industrial-scale fabrication, financial schemes for required instruments, patient compliance administration and high adaptability to human diverse pharmacokinetics.

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