REVIEW

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Lipid-Based Nanocarriers for Oral Drug Delivery: Advances, Challenges and Clinical Prospects

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ABSTRACT

Lipid-based nanocarriers have gained significant attention in oral drug delivery due to their ability to enhance solubility, bioavailability, and therapeutic efficacy of poorly water-soluble drugs. Among these, Solid Lipid Nanoparticles (SLNs) and Nanostructured Lipid Carriers (NLCs) are widely explored for their controlled drug release, stability, and improved absorption via mechanisms such as lymphatic transport and mucus penetration. Recent advancements, including surface modifications (PEGylation), functionalization with bioadhesive ligands, and pH-sensitive lipid formulations, have further improved their performance. However, challenges related to stability, large-scale manufacturing, and regulatory approval remain critical barriers to clinical translation. Several lipid-based formulations have already entered clinical trials, demonstrating potential in treating cancer, diabetes, and infectious diseases. Future research should focus on novel lipid excipients, personalized drug formulations, and advanced manufacturing techniques to facilitate the commercialization of these nanocarriers. This review highlights the latest advancements, challenges, and future prospects of lipid-based nanocarriers for efficient and patient-friendly oral drug delivery systems

KEYWORDS: Lipid-based nanocarriers, oral drug delivery, bioavailability enhancement, targeted drug delivery, clinical applications.

INTRODUCTION

Oral drug delivery is the most convenient, non-invasive, and patient-friendly method of drug administration, making it the preferred route for most pharmaceutical formulations.(1) However, despite its advantages, oral drug delivery presents significant challenges, particularly for drugs with poor aqueous solubility, low permeability, or susceptibility to enzymatic degradation in the gastrointestinal (GI) tract.(2) The biopharmaceutical classification system (BCS) categorizes drugs based on solubility and permeability, with BCS Class II (low solubility, high permeability) and Class IV (low solubility, low permeability) drugs facing the greatest barriers to oral absorption.(3) To address these challenges, researchers have developed various drug delivery systems, among which lipid-based nanocarriers have emerged as a promising approach.(4)

Lipid-based nanocarriers, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), offer numerous advantages over conventional drug delivery systems.(5) These nanocarriers can enhance drug solubility, protect drugs from enzymatic degradation, improve intestinal permeability, and promote lymphatic transport, thereby increasing the systemic bioavailability of orally administered drugs.(6) Additionally, lipid-based nanocarriers allow for controlled and sustained drug release, reducing dosing frequency and improving patient adherence to treatment.(7)

SLNs, composed of solid lipids stabilized by surfactants, provide a stable and biocompatible drug delivery platform with the potential for targeted and controlled drug release.(8) However, limitations such as low drug-loading capacity and polymorphic transitions have led to the development of NLCs, which incorporate both solid and liquid lipids to enhance drug encapsulation efficiency and stability. These advancements have made lipid-based nanocarriers an attractive option for oral drug delivery, particularly for lipophilic drugs with poor aqueous solubility.(9)

Given the growing interest in lipid-based nanocarriers, this review explores the latest advancements, challenges, and clinical prospects of SLNs and NLCs in oral drug delivery.(10) The discussion will focus on their formulation strategies, mechanisms of bioavailability enhancement, potential limitations, and recent clinical applications. Understanding these aspects is essential for the continued development and commercialization of lipid-based nanocarriers as an effective solution for improving oral drug delivery.(11)

1. Types of Lipid-Based Nanocarriers

Lipid-based nanocarriers have gained significant attention in the field of pharmaceutical sciences due to their ability to enhance the solubility, stability, and bioavailability of poorly water-soluble drugs. These nanocarriers are biocompatible, improve drug protection from enzymatic degradation, and facilitate controlled drug release. Among them, solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs) are the most widely explored for oral drug delivery.(9)

1.1 Solid Lipid Nanoparticles (SLNs)

Solid lipid nanoparticles (SLNs) are colloidal drug delivery systems composed of solid lipids that remain solid at both room and body temperatures. These lipids can include triglycerides, glyceride mixtures, fatty acids, or waxes, and are stabilized by surfactants such as lecithin, poloxamers, or sodium dodecyl sulfate.(12)

Advantages of SLNs

- **Protection from enzymatic and chemical degradation**: The solid lipid core acts as a protective barrier, preventing premature drug breakdown in the harsh gastrointestinal (GI) environment.
- **Controlled and sustained drug release**: SLNs offer prolonged drug release due to the solid-state lipid matrix, reducing dosing frequency and enhancing patient adherence.
- **Enhanced bioavailability**: SLNs improve drug solubility and absorption, particularly for hydrophobic drugs that struggle with poor water solubility.

High biocompatibility: Composed of physiological lipids, SLNs are generally safe for oral administration.(13)

Limitations of SLNs

- **Low drug-loading capacity**: The highly ordered crystalline structure of solid lipids limits the amount of drug that can be encapsulated.
- **Polymorphic transitions**: Changes in lipid crystal structure over time can lead to drug expulsion, affecting formulation stability.

Potential aggregation and gelation: Under certain conditions, SLNs may aggregate, leading to stability issues during storage. (14)

1.2 Nanostructured Lipid Carriers (NLCs)

Nanostructured lipid carriers (NLCs) were developed as an improvement over SLNs. Unlike SLNs, which contain only solid lipids, NLCs incorporate a mixture of solid and liquid lipids, resulting in a less ordered lipid matrix. This modification significantly enhances drug-loading capacity and stability. (5)

Advantages of NLCs

- **Higher drug-loading capacity**: The presence of liquid lipids creates more amorphous spaces within the lipid matrix, allowing greater drug entrapment.
- **Reduced crystallinity**: The less ordered structure minimizes drug expulsion, improving long-term stability.
- **Better physicochemical stability**: NLCs exhibit reduced risk of aggregation and gelation compared to SLNs.

More efficient drug absorption: The lipid composition of NLCs improves solubilization and intestinal permeability, leading to enhanced bioavailability.(15)

Limitations of NLCs

- **Complex formulation process**: The inclusion of both solid and liquid lipids makes the preparation of NLCs more technically demanding.
- **Potential phase separation**: Certain lipid combinations may cause phase separation, reducing drug retention efficiency. (15)

Both SLNs and NLCs hold significant promise for oral drug delivery, with NLCs offering superior drug-loading capacity and stability. The choice between these two systems depends on the drug's physicochemical properties and the desired release profile.

2. **Mechanism of Drug Absorption and** Bioavailability Enhancement

Lipid-based nanocarriers enhance drug absorption and bioavailability through multiple mechanisms, making them particularly beneficial for oral drug delivery. These mechanisms include enhanced solubilization, lymphatic transport, and mucus penetration, all of which contribute to improved drug uptake and therapeutic efficacy.(16)

2.1 Enhanced Solubilization

One of the major limitations of oral drug administration is poor

aqueous solubility, which leads to insufficient drug dissolution in the gastrointestinal tract and reduced absorption. Lipid-based nanocarriers address this issue by:

- **Encapsulating lipophilic drugs within lipid matrices**, which increases their apparent solubility in gastrointestinal fluids.

- **Facilitating micelle and mixed micelle formation**: When lipids in the formulation interact with **bile salts and phospholipids in the intestine**, they form **mixed micelles**, which enhance drug solubilization and transport.

Reducing drug crystallinity: The presence of liquid lipids in NLCs lowers the crystallinity of the drug, resulting in **faster dissolution and improved absorption**.(17)

2.2 Lymphatic Transport

A key advantage of lipid-based nanocarriers is their ability to **bypass hepatic first-pass metabolism** by utilizing the **intestinal lymphatic system**. This mechanism is particularly beneficial for **lipophilic drugs that undergo extensive liver metabolism**, as it results in:

- **Increased systemic drug levels**, leading to improved bioavailability.

- **Reduced drug degradation**, prolonging circulation time and enhancing therapeutic effects.

Higher drug accumulation at the target site, particularly useful for drugs with low oral bioavailability.(18)

Mechanism of Lymphatic Transport

- Lipid-based nanocarriers **stimulate chylomicron formation** in the intestine, which facilitates drug transport into the **lymphatic circulation** instead of the portal vein.

- The presence of **long-chain triglycerides (LCTs)** in the lipid matrix enhances **drug association with chylomicrons**, promoting **lymphatic absorption**.

Lymphatic uptake bypasses hepatic metabolism, allowing a greater proportion of the drug to reach systemic circulation intact.(18)

2.3 Mucus Penetration

The mucus layer in the gastrointestinal tract serves as a protective barrier against foreign particles, often hindering drug absorption. Lipid-based nanocarriers improve drug penetration through the mucus layer via:

- **Small particle size**: Nanoparticles with diameters below 200 nm can more easily diffuse through the mucus network.

- **Surface modification with hydrophilic polymers**: Coating lipid nanoparticles with polyethylene glycol **(**PEGylation**)** or other hydrophilic agents helps them evade mucus entrapment and clearance, increasing residence time.

Bioadhesive properties: Certain lipid formulations exhibit mucoadhesion, allowing the nanoparticles to adhere to the intestinal epithelium, leading to prolonged contact time and improved drug absorption.(19)

Overall Impact on Oral Bioavailability

By combining these mechanisms, lipid-based nanocarriers effectively overcome physiological barriers in the gastrointestinal tract and enhance drug bioavailability. This makes them a highly promising approach for improving oral delivery of poorly water-soluble and lipophilic drugs.(20)

3. Advances in Lipid-Based Nanocarrier Formulations

The field of lipid-based nanocarriers has witnessed significant advancements in recent years, aiming to enhance their stability, bioavailability, and targeted drug delivery. Researchers have explored various modifications to optimize drug loading, prolong circulation time, and improve absorption in the gastrointestinal (GI) tract. Some of the most notable advancements include surface modification with polymers (PEGylation), functionalization with bioadhesive ligands, and the development of pH-sensitive lipid carriers for site-specific drug release.(21)

3.1 Surface Modification with Polymers (PEGylation)

One of the major limitations of traditional lipid-based nanocarriers is their susceptibility to premature degradation and clearance in the GI tract. To overcome this, researchers have employed polymer-based surface modifications, with polyethylene glycol **(**PEGylation**)** being the most widely used approach.

Benefits of PEGylation in Lipid-Based Nanocarriers

- **Improved Stability**: PEGylation forms a hydration shell around the nanoparticle, preventing aggregation and enzymatic degradation in the GI environment.

- **Prolonged Circulation Time**: PEGylated nanoparticles exhibit a stealth effect**,** reducing their recognition by the mononuclear phagocyte system (MPS) and allowing for extended systemic circulation.

- **Enhanced Mucus Penetration**: The hydrophilic nature of PEG enables nanoparticles to diffuse through the mucus layer, facilitating better absorption across the intestinal epithelium.

Reduced Protein Adsorption: PEGylation minimizes the adsorption of plasma proteins (opsonization), preventing nanoparticle clearance by immune cells.(22)

Applications of PEGylated Lipid Nanocarriers

PEGylated SLNs and NLCs have been explored for the oral delivery of anticancer drugs, peptides, and poorly water-soluble compounds. For example, PEGylated lipid nanoparticles loaded with paclitaxel have demonstrated improved oral bioavailability and prolonged drug release, making them a promising alternative to intravenous chemotherapy.(23)

3.2 Functionalization with Bioadhesive Ligands

To further enhance intestinal uptake, lipid-based nanocarriers can be functionalized with bioadhesive ligands, allowing them to adhere to the intestinal mucosa for prolonged retention and increased absorption.(24)

Key Bioadhesive Ligands Used in Lipid-Based Nanocarriers

- **Chitosan**: A **positively charged polysaccharide** that interacts with negatively charged mucins, enhancing adhesion and permeability.

- **Lectins**: Carbohydrate-binding proteins that selectively bind to intestinal epithelial cells, facilitating **receptor-mediated endocytosis** of drug-loaded nanocarriers.

Hyaluronic Acid: A natural polymer that interacts with CD44 receptors on enterocytes, promoting nanoparticle uptake.

Advantages of Bioadhesive Ligand Functionalization

- **Prolonged Retention in the GI Tract**: Increases the likelihood of drug absorption by maintaining close contact with intestinal cells.

- **Improved Cellular Uptake**: Facilitates endocytosis and transcytosis, leading to **higher drug transport across the intestinal barrier**.

Enhanced Targeting and Specificity: Functionalization with ligands enables **site-specific drug delivery**, reducing off-target effects.(25)

Applications of Bioadhesive Lipid-Based Nanocarriers

Bioadhesive SLNs and NLCs have been extensively investigated for **oral insulin delivery**, where they improve insulin absorption and bioavailability by **increasing residence time and preventing enzymatic degradation**.(6)

3.3 pH-Sensitive Lipid Carriers for Targeted Drug Release

A major challenge in oral drug delivery is ensuring drug release at the desired site in the GI tract**,** as different regions exhibit varying pH conditions. pH-sensitive lipid carriers are designed to respond to these pH changes**,** triggering drug release at specific intestinal locations**.**

Mechanism of pH-Sensitive Lipid Carriers

- **Acidic pH in the Stomach (pH ~1.5–3.5)**: The drug re-

Table 1. Approved and Clinically Investigated Lipid-Based Nanocarriers (34)(35)(36)(37)

Drug	Lipid-Based Formulation	Indication	Clinical status
Cyclosporine A	Neoral® (Self-emulsifying lipid formulation)	Immunosuppressant for organ transplantation	FDA Approved
Saquinavir	Fortovase® (Lipid-based soft gel)	HIV/AIDS treatment	FDA Approved
Fenofibrate	Triglide® (Lipid microparticle formulation)	Hyperlipidemia	FDA Approved
Paclitaxel	Nanoxel® (Lipid-based nanocarrier)	Cancer therapy	Clinical Trials

mains encapsulated within the lipid matrix, preventing premature degradation.

Neutral to Slightly Alkaline pH in the Small Intestine (pH ~6–7.4): The lipid carrier undergoes structural changes or dissolution, **triggering drug release** for enhanced absorption.(26)

Types of pH-Sensitive Lipid Carriers

1. **pH-Responsive Polymers**: Lipid-based nanoparticles coated with pH-sensitive polymers (e.g., **Eudragit**, **poly (methacrylic acid)**) dissolve at higher pH, ensuring drug release in the intestine.

2. **pH-Responsive Lipids**: Some lipids, such as **fatty acid derivatives**, undergo **pH-induced phase transitions**, enabling site-specific drug release.

Enteric-Coated Lipid Nanoparticles: SLNs and NLCs coated with enteric materials protect drugs from gastric degradation and dissolve in the small intestine for **targeted release**.

Advantages of pH-Sensitive Lipid Carriers

- **Protection from Gastric Degradation**: Ensures the stability of acid-labile drugs (e.g., **proteins, peptides, and probiotics**) in the stomach.

- **Site-Specific Drug Release**: Improves drug absorption at the optimal site, reducing dose requirements and potential side effects.

Enhanced Drug Bioavailability: pH-triggered release ensures **maximum drug absorption in the intestine**, leading to **higher systemic drug concentrations**.

Applications of pH-Sensitive Lipid-Based Nanocarriers

pH-sensitive lipid carriers have shown promise in the oral delivery of antibiotics (e.g., amoxicillin for H. pylori infection) and biologics (e.g., insulin, vaccines)**,** ensuring optimal drug release and improved therapeutic outcomes.(27)

4. Challenges and Limitations of Lipid-Based Nanocarriers

Despite their numerous advantages, lipid-based nanocarriers still face several challenges and limitations that hinder their widespread clinical application.(28) These challenges include stability issues, difficulties in large-scale manufacturing, and regulatory hurdles that must be addressed to ensure consistent, safe, and effective drug formulations.(29)

4.1 Stability Issues

One of the major concerns with lipid-based nanocarriers is their physicochemical stability**,** which can significantly affect drug loading, release profiles, and therapeutic efficacy. The two primary stability challenges are lipid oxidation and polymorphic transitions.(30)

Lipid Oxidation

- Lipids, particularly **unsaturated fatty acids**, are prone to oxidation when exposed to **oxygen, light, and heat**.

- Lipid oxidation can lead to **rancidity, degradation of encapsulated drugs, and altered physicochemical properties**, potentially reducing bioavailability.

- Strategies to prevent oxidation include:

o **Using antioxidants** (e.g., α-tocopherol, butylated hydroxytoluene).

o **Storing formulations under inert gas (e.g., nitrogen or argon)** to minimize oxygen exposure.

Encapsulation in protective coatings to shield lipids from environmental factors.(31)

Polymorphic Transitions

- Lipids can exist in different **crystalline forms (polymorphs)**, and transitions between these forms can **affect drug stability and release**.

Table 2 Emerging Manufacturing Technologies(43)(44)(45)(46)

Technology	Benefits
Microfluidics	Precise control over particle size and composition.
High-pressure homogenization	Scalable and reproducible nanoparticle synthesis.
Spray drying and electrospraying	Improves powder formulation stability.
Nanoprecipitation	Cost-effective and environmentally friendly lipid nanoparticle synthesis.

- Over time, **lipids may rearrange into more stable crystalline forms**, leading to **drug expulsion** from the nanoparticle matrix.

- Strategies to minimize polymorphic transitions include:

o Using a **combination of solid and liquid lipids** (as in NLCs) to **reduce crystallinity**.

o Selecting lipids with **low polymorphic transition tendencies**, such as tristearin or glyceryl monostearate.

Incorporating **surfactants and stabilizers** (e.g., Poloxamer 188, lecithin) to maintain lipid structure.(4)

4.2 Manufacturing Scalability and Reproducibility

While lipid-based nanocarriers show promising results in preclinical and small-scale studies, translating these formulations to large-scale commercial production presents significant challenges.

Key Manufacturing Challenges

- **Complex and time-consuming preparation methods**: Techniques such as high-pressure homogenization, microemulsification, and solvent evaporation require precise control over temperature, pressure, and mixing to maintain nanoparticle size and stability.

- **Batch-to-batch variability**: Differences in raw material quality, lipid composition, and processing conditions can result in inconsistent drug loading, particle size, and release profiles.

- **High production costs**: The use of specialized equipment, sterile processing conditions, and complex formulation steps increases manufacturing costs.

Poor long-term storage stability: Liquid formulations may suffer from aggregation, coalescence, or drug leakage**,** necessitating the development of freeze-dried (lyophilized) formulations**,** which further complicates processing.

Strategies to Overcome Manufacturing Challenges

- **Standardizing lipid and surfactant selection** to minimize variability.

- **Developing scalable, continuous manufacturing processes** (e.g., microfluidic technology) to improve efficiency and reproducibility.

- **Optimizing freeze-drying protocols** using cryoprotectants (e.g., trehalose, mannitol) to improve long-term stability.

Automating nanoparticle synthesis to improve consistency and reduce human error.(32)

4.3 Regulatory Hurdles

The approval process for lipid-based nanocarriers is **more complex than conventional drug formulations**, as these systems involve multiple **components (lipids, surfactants, stabilizers) that can affect drug performance**.

Regulatory Challenges

- **Variability in lipid composition**: Unlike small-molecule drugs, lipid-based formulations may contain natural or synthetic lipids with batch-to-batch variations, leading to challenges in defining quality control parameters.

- **Lack of standardized regulatory guidelines**: While traditional pharmaceuticals follow well-established guidelines (e.g., ICH, FDA, EMA)**,** lipid-based nanocarriers often fall under nanomedicine regulations, which are still evolving.

- **Toxicological concerns**: Although lipids are generally regarded as safe **(**GRAS**),** certain surfactants, solvents, or lipid degradation products may pose long-term toxicity risks.

Bioequivalence challenges: Nanocarriers often alter drug pharmacokinetics, making it difficult to establish bioequivalence with conventional formulations, complicating regulatory approval.

Strategies to Overcome Regulatory Hurdles

- Establishing clear quality control parameters, including particle size, zeta potential, encapsulation efficiency, and drug release kinetics.

- Conducting extensive safety studies to evaluate the long-term effects of lipid-based carriers on the liver, kidneys, and immune system.

- Collaborating with regulatory agencies (FDA, EMA) to develop standardized evaluation criteria for lipid-based drug delivery systems.

Using well-characterized excipients (e.g., FDA-approved li-

pids and surfactants) to streamline the approval process.(33)

5. Clinical Applications and Future Prospects of Lipid-Based Nanocarriers

Lipid-based nanocarriers have shown significant potential in clinical applications, particularly in enhancing drug solubility, bioavailability, and targeted delivery. Several formulations have successfully progressed to clinical trials and commercial products, demonstrating improved therapeutic efficacy, patient compliance, and reduced side effects. However, challenges remain in optimizing these systems for widespread clinical adoption.(4) Future research and development should focus on novel lipid excipients, personalized therapies, and scalable manufacturing techniques to ensure the commercial viability of these advanced drug delivery platforms.(9)

5.1 Clinical Applications of Lipid-Based Nanocarriers

Lipid-based nanocarriers are being extensively investigated for the oral delivery of poorly water-soluble drugs, peptides, and biologics. Several formulations have already reached clinical trials or the market, proving their efficacy and safety in treating various diseases.

Key Therapeutic Areas Benefiting from Lipid-Based Nanocarriers

- **Cancer Therapy**: Lipid-based nanocarriers improve the solubility and bioavailability of poorly water-soluble anticancer drugs (e.g., paclitaxel, doxorubicin), reducing systemic toxicity and enhancing tumor targeting.

- **Diabetes Management**: Oral insulin-loaded lipid nanoparticles are being explored to replace injectable insulin, improving patient compliance.

- **Neurodegenerative Disorders**: Lipid nanocarriers enhance the brain bioavailability of drugs used in Alzheimer's and Parkinson's disease via lipid-mediated transport across the blood-brain barrier (BBB).(38)

- **Infectious Diseases**: Lipid-based formulations improve the absorption and efficacy of antiviral (saquinavir, ritonavir) and antibacterial drugs (rifampicin, amoxicillin for H. pylori infection).(39)

Cardiovascular Disorders: Lipid-based nanocarriers enhance the delivery of antihyperlipidemic and antihypertensive drugs, ensuring better solubility and bioavailability.(4)

5.2 Future Prospects in Lipid-Based Nanocarrier Research

To overcome current challenges and expand their clinical applications, future research should focus on **enhancing stability, improving targeted delivery, and optimizing large-scale production**. Key areas of development include:

5.2.1 Novel Lipid Excipients for Enhanced Stability and Bioavailability

The choice of lipids and excipients plays a crucial role in the performance of lipid-based nanocarriers. (24) Future advancements should focus on identifying and engineering novel lipid components that provide:

- Better chemical and physical stability to prevent lipid oxidation and polymorphic transitions**.**

- Higher drug loading capacity, improving therapeutic efficacy.

- Improved interaction with biological membranes, leading to enhanced drug permeability and absorption.

pH-responsive and stimuli-sensitive lipids for controlled and site-specific drug release in the gastrointestinal (GI) tract. (10)

Examples of Emerging Lipid Excipients

- **Modified phospholipids** with enhanced stability.

- **Glyceride-based lipids** for better drug encapsulation.

Lipid-polymer hybrid carriers combining the advantages of both lipid and polymeric nanocarriers.(40)

5.2.2 Personalized Lipid Formulations for Targeted Therapies

With the advancement of **personalized medicine**, future research should focus on developing **customized lipid-based formulations** tailored to an individual's genetic profile, disease condition, and metabolism.

Key Approaches for Personalized Lipid-Based Nanocarriers

- **Precision Nanomedicine**: Designing lipid nanoparticles that are optimized for a patient's drug metabolism and absorption profile**.**

- **Ligand-Targeted Lipid Carriers**: Functionalizing lipid nanoparticles with antibodies, peptides, or aptamers to selec-

tively target diseased tissues (e.g., tumors, inflamed sites).

- **3D Printing of Lipid-Based Dosage Forms**: Using 3D printing technology to fabricate patient-specific lipid-based oral drug formulations for precise dosing.

Artificial Intelligence (AI)-Driven Formulation Development: Leveraging AI and machine learning to optimize lipid compositions, particle sizes, and drug release profiles based on patient data.(41)

Applications of Personalized Lipid Formulations

- **Targeted chemotherapy** with lipid carriers that selectively bind to tumor cells.

- **Custom lipid-based insulin delivery** systems optimized for an individual's glucose metabolism.

Personalized lipid formulations for neurological disorders, improving blood-brain barrier permeability based on a patient's genetic markers.(42)

5.2.3 Improved Large-Scale Manufacturing Techniques for Commercial Viability

One of the biggest hurdles in translating lipid-based nanocarriers from research to commercial production is manufacturing scalability and cost-effectiveness. Future advancements should focus on:

Key Improvements in Manufacturing

- **Continuous Manufacturing Processes**: Replacing batch production with **automated, high-throughput techniques** for consistent and scalable production.

- **Green and Sustainable Synthesis**: Developing **solvent-free and eco-friendly** lipid formulation methods to reduce environmental impact.

- **Advanced Nanoparticle Engineering**: Using **microfluidics and electrospraying** for precise control over nanoparticle size and drug loading.

Lyophilization (Freeze-Drying) Optimization: Enhancing **long-term storage stability** of lipid-based formulations for better commercial viability.(11)

Conclusion

Lipid-based nanocarriers have emerged as a revolutionary approach in oral drug delivery, offering enhanced solubility, bioavailability, and targeted therapeutic effects. Various types, including Solid Lipid Nanoparticles **(SLNs)** and Nanostructured Lipid Carriers (NLCs), have shown promising results in improving drug absorption through mechanisms like lymphatic transport, mucus penetration, and enhanced solubilization. Despite these advantages, challenges such as stability issues, large-scale manufacturing complexities, and regulatory hurdles must be addressed to ensure their widespread clinical adoption. Recent advancements, including surface modifications, novel lipid excipients, and personalized lipid formulations, are helping to overcome these limitations. Several lipid-based formulations have already reached clinical trials and commercial markets, proving their potential in treating various diseases, including cancer, diabetes, neurodegenerative disorders, and infectious diseases. Future research should focus on innovative manufacturing techniques, AI-driven formulation development, and targeted therapies to further optimize these systems. Lipid-based nanocarriers represent a promising future for oral drug delivery, and with continued advancements, they are set to **redefine pharmaceutical formulations**, making therapies **more effective, patient-friendly, and commercially viable.**

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