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Lipid-Based Nanocarriers for Oral Delivery of Poorly Soluble Drugs

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Abstract

The oral route is still the most desirable route of drug delivery because of its ease of use, patient compliance and cost, but there is a major limitation regarding poor solubility of many therapeutic compounds in aqueous medium, therefore, this limits the oral delivery of the drug and clinical outcome. Solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs), as well as self-emulsifying drug delivery systems (SEDDS), are the latest approaches to address these shortcomings. The nanoscales protect labile compounds against degraded by gastrointestinal system, increase solubility of drugs, and facilitate absorption via lymphatic system bypassing first-pass metabolism. Preclinical and animal experiments have demonstrated that SLNs give sustained release and gastrointestinal protection, NLCs give drug loading, stability and controlled release, and SEDDS gives dissolution, systemic exposure and lymphatic uptake. Another advantage of LNCs is better tissue distribution, extended circulation, ameliorated pharmacokinetic and pharmacodynamic activity. Regardless of their promise, such challenges as formulation stability, large scale production, interspecies translational differences, and excipient safety are critical factors. Altogether, LNCs provide a versatile and promising system of creation of effective patient-friendly oral preparations of drugs that are hardly soluble, and their possible clinical translation and specific treatment use have significant potential.

Key Words:

Lipid-Based Nanocarriers, Solid Lipid Nanoparticles, Nanostructured Lipid Carriers, Self-Emulsifying Drug Delivery Systems, Poorly Soluble Drugs, Oral Bioavailability, Lymphatic Transport, Drug Stability.

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1. INTRODUCTION

The oral drug delivery is the most desirable method of administration because it is convenient, acceptable by the patient and is cost-effective. Nevertheless, one major problem in contemporary pharmaceutics is that the aqueous solubility of most therapeutic agents is such that their

bioavailability by the oral route and therapeutic action is limited[1]. Drugs with low solubility tend to have low gastrointestinal absorption, high first-pass metabolism, and unpredictable pharmacokinetics, as well as, it becomes hard to achieve consistent plasma levels. Conventional methodologies, including reduction of particle size, salt formation and dissolution of excipients, have demonstrated poor attempts to overcome these obstacles. Here lipid-based nanocarriers such as SLNs, NLCs, and SEDDS have become the most promising method to improve solubility and stability as well as oral bioavailability of poorly soluble drugs.

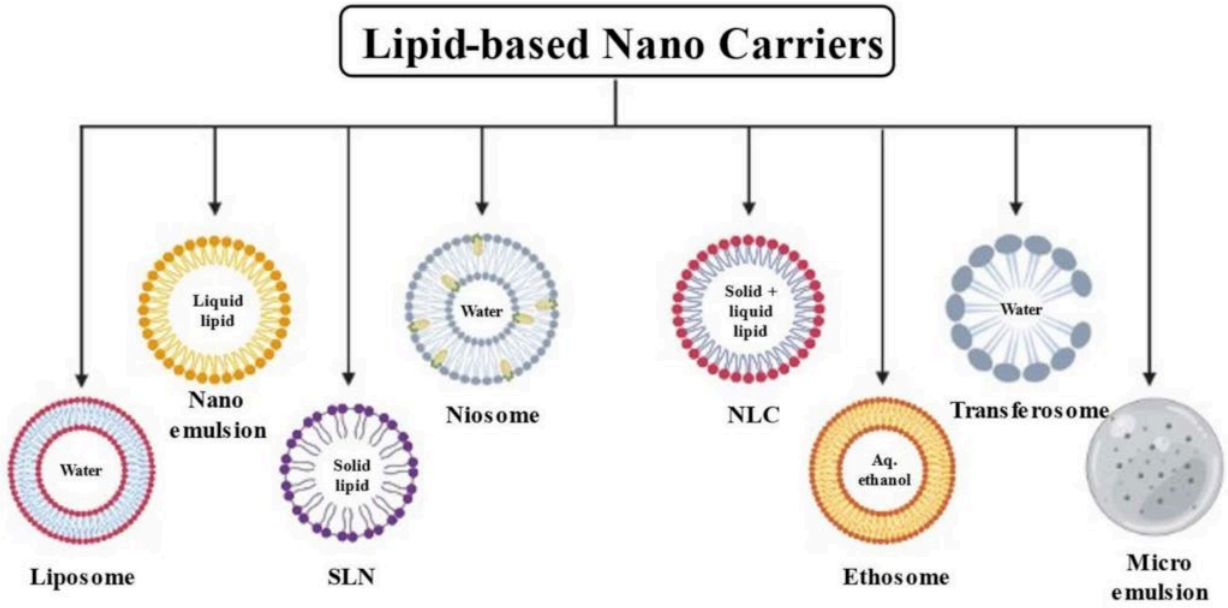

Figure 1: Lipid Based Nano Carriers[2]

Lipid nanocarriers have a number of benefits in terms of delivery of oral drugs. They are able to entrap hydrophobic drugs into a biocompatible lipid, shield them against degradation by the gastrointestinal environment, and transport them across the intestinal lymphatic system thereby avoiding first-pass metabolism. Moreover, LNCs are capable of delivering sustained or controlled release, enhanced pharmacokinetics and targeted tissue distribution. The effectiveness of the systems in improving the bioavailability of drugs, the circulation time, and the therapeutic effects was well supported by animal studies and preclinical research. The feasibility, shortcomings and mechanistic nature of lipid based nanocarriers are hence important in translating successfully into the clinical set ups[3].

a. Background Information and Context

The creation of lipid-based nanocarriers is a breakthrough in the design of drugs that have low solubility. These nano systems are used to increase drug solubility rates, prevent the degradation of labile drug compounds, and enhance absorption through the gastrointestinal tract by using lipid matrices. Various forms of lipids nanocarriers, including SLNs, NLCs, and SEDDS, have distinct structural and functional characteristics that determine the drug loading capacity, release kinetic and pharmacokinetic characteristics[4]. The interest of this field has increased significantly in the last decade as a result of the growing popularity of hydrophobic drugs in contemporary medicine and the shortcomings of traditional oral preparations.

b. Objectives of the Review

- To evaluate the role of lipid-based nanocarriers in enhancing the oral bioavailability of poorly soluble drugs.
- To summarize preclinical and animal-based evidence demonstrating improvements in drug solubility, absorption, pharmacokinetics, and tissue distribution using LNCs.
- To critically analyze the strengths, limitations, and formulation-specific challenges associated with SLNs, NLCs, and SEDDS.
- To assess the mechanisms by which LNCs bypass first-pass metabolism, enhance lymphatic transport, and provide sustained or controlled drug release.
- To identify research gaps and suggest future directions for clinical translation, scalable production, and safe long-term application of lipid-based nanocarriers.

c. Importance of the Topic

Increasing the oral bioavailability of drugs with low solubility has great patient outcomes implications, therapeutic efficacy, and pharmaceutical development. Lipid nanocarriers can overcome the difficulties of solubility, as well as have potential to deliver therapeutics in a targeted manner, with a prolonged release, and less frequent dosing[5]. LNCs can be used in order to increase the systemic exposure and tissue distribution that can increase the therapeutic index of drugs and reduce side effects. In its turn, this field of study is essential in the evolution of the oral drug delivery technologies and the creation of more efficient and less invasive methods of therapeutic intervention.

2. PRECLINICAL EVIDENCE, METHODOLOGIES, AND CRITICAL EVALUATION OF LIPID-BASED NANOCARRIERS (LNCS)

Animal studies demonstrate that lipid-based nanocarriers (LNCs) greatly improves solubility, absorption, and pharmacokinetics of poorly soluble drugs, due to an increase in bioavailability, stability, and lymphatic absorption. However, challenges related to large-scale production, clinical translation and long-term stability of LNCs still represent major challenges towards their commercial and therapeutic use[6].

a. Summary of Key Research Studies

It has been found in animal studies that there are always better pharmacokinetics of poorly soluble drugs in case of lipid nanocarriers (LNCs). These researches indicate that SLNs, NLCs and SEDDS can help improve the solubility and absorption of drugs. For example:

1. Compared to the pure curcumin suspensions, curcumin-loaded SLNs which were administered orally to rats showed a significant enhancement in plasma concentration and bioavailability in general. This was accredited to the protective lipid environment and enhanced solubilization; this enhanced absorption across the gastrointestinal tract[7].

2. The SEDDS formulation of cyclosporine exhibited a dramatic improvement in the lymphatic delivery and systemic exposure in the dogs. The lipid-based self-emulsifying system enhances dissolution and also enables easy circumvention of the hepatic first-pass metabolism which results in an excellent pharmacokinetic outcome.

3. The NLCs loaded with quercetin demonstrated an extended circulation time and tissue distribution in mice than the traditional quercetin preparations. This addition of solid and liquid lipids to NLCs led to increased entrapment of the drug, prolonged release and increased stability of NLCs in circulation by the body.

b. Methodologies and Findings

Rodent models (rats, mice) that were used in most studies to preliminary assess pharmacokinetic properties were the rat models that are cheaper to use and can detect the drug properties at an early stage, whereas canine models were commonly used to specifically determine lymphatic transport pathways[8]. The main experimental methods were pharmacokinetic profiling by examining blood plasma, biodistribution by labeled preparations and stability by observing drug retention in lipid matrices. The results were consistently shown to result in improved Cmax, improved AUC and increased half-life, which all presented improved drug absorption, prolonged circulation and decreased clearance.

c. Strengths and Weaknesses

Lipid-based nanocarriers (LNCs) are an efficient delivery method in that they increase bioavailability, avoid the issue of first-pass metabolism, and enhance the stability of drugs during oral delivery. Nevertheless, their clinical and commercial potential are capped by issues of scalability, pharmacokinetic translation and long-term stability[9].

- **Strengths:** Nanocarriers Lipid-based nanocarriers (LNCs) have shown a consistent increase in bioavailability in diverse delivery systems, which has indicated that LNCs are versatile in the enhancement of poorly soluble drugs. One of the benefits of LNCs is that the bypass first-pass metabolism by lymphatic uptake, resulting in augmentation of the systemic exposure of the drug and reducing hepatic degradation. Moreover, these carriers provide stability to drugs by entrap compounds within lipid matrices not only protecting delicate drugs against degradation in the gastrointestinal tract, but also helping drugs to possess a long shelf life, rendering them very useful in delivering drugs orally[10].
- **Weaknesses:** Lipid-based nanocarriers (LNCs) have a number of drawbacks even though they hold promise, and these limitations limit their clinical translation and use in large-scale applications. Their commercial viability has not been addressed by challenges with reproducibility of formulations and scalable manufacturing. Besides, the weak association between animal and human pharmacokinetics makes it difficult to predict the therapeutic outcomes in clinical practice. Stability problems also contribute to these issues, with leakage of drugs, polymorphic changes of lipids, and aggregation of nanoparticles potentially impacting performance negatively and long-term storage compromise, which has placed increased emphasis on improved design and standardization solutions[11].

3. LIPID-BASED NANOCARRIERS: SLNS, NLCS, AND SEDDS

Lipid based nanocarriers, SLNs, NLCs, SEDDS are used to increase oral bioavailability of poorly soluble drugs, by increasing solubility, absorption and stability. SLNs offer long-term release and prevent degradation of drugs by the gastrointestinal tract but can experience stability problems because of polymorphic transitions[12]. Combining solid and liquid lipids, NLCs have better drug loading capacities, release control, and enhance long-term stability. SEDDS are small emulsions that are created in the gut where they increase the chances of dissolution and circumvent the first-pass metabolism, but excipient selection must be done carefully to prevent gastrointestinal toxicity.

a. Solid Lipid Nanoparticles (SLNs)

SLNs are an emerging method of drug delivery which is based on lipid biomaterials and could be used in oral delivery of drugs that have low bioavailability. Research in rats demonstrated that SLNs have the potential to enhance the absorption of hydrophobic drugs like curcumin and paclitaxel to a great extent[13]. The latter is mainly credited to the fact that the drugs are encapsulated into a lipid-based biocompatible solid matrix that ensures a solubilization besides offering a sustained release effect. Because of this, therapeutic plasma levels are able to be sustained over extended periods of time than their traditional drug counterparts. Furthermore, the structural stiffness of lipids is additional protection against enzymatic degradation within the gastrointestinal tract, which leads to a better stability and effect of the drug.

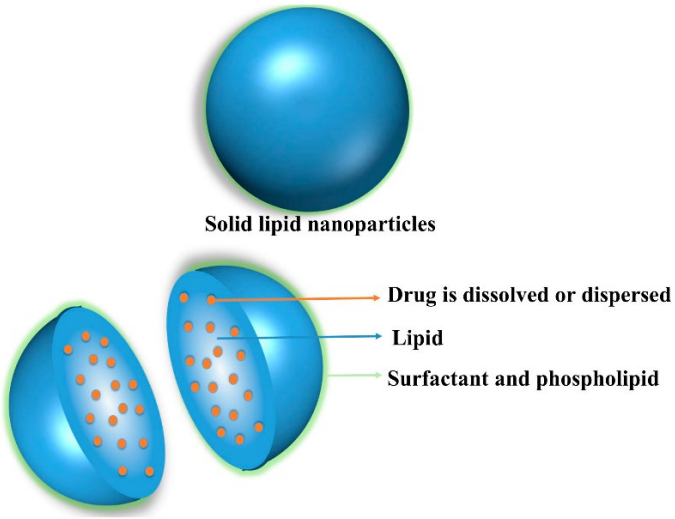

Figure 2: Solid Lipid Nanoparticles (SLNs)[14]

Although SLNs have their benefits, they still pose several issues with formulation and stability that may impede their long-term applications. An issue that might eventually require attention is the polymorphic transitions of the lipid matrix, as these transitions can give rise to changes in the crystallinity of nanoparticles resulting in potential bulk structural instability and expulsion of drug during storage[15]. Changes in structural properties of SLNs can lead to compromised drug loading efficiency, which can ultimately lead to diminished therapeutic effect over time. Thus, lipid selection, characterization, and optimized formulation strategies is important for reproducibility, stability, and clinical benefit of SLN-based drug delivery systems.

b. Nanostructured Lipid Carriers (NLCs)

NLCs are the 2nd-generation lipid-based nanocarriers and have been developed with the aim of overcoming problems associated with SLNs. NLCs consist of both solid and liquid lipids and form an "imperfect" crystalline matrix providing better drug loading capacity and reduced risk of drug expulsion during storage. With its structural and design, NLCs not only improved encapsulation efficiency but provided more controlled and sustained drug release. In mice, quercetin-loaded NLCs had improved antioxidant activity and improved tissue distribution compared to conventional formulations, indicating the potential usefulness of NLCs for therapeutic applications requiring systemic circulation and targeted drug delivery[16].

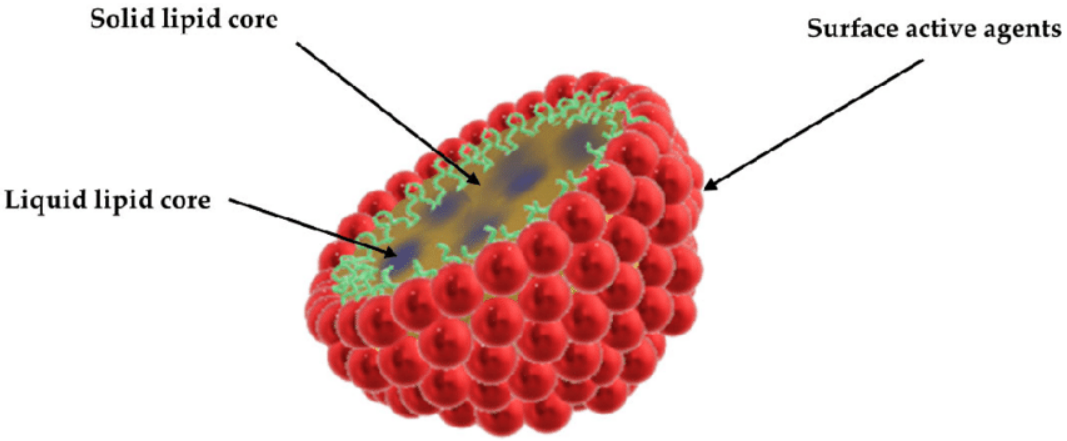

Figure 3: Nanostructured Lipid Carriers (NLCs)[17]

NLCs remain stable over a long period because of the inclusion of liquid lipids, which reduce instability caused by crystallization, in addition to their ability to increase drug loading and release properties. Such a malleability of the lipid matrix minimizes the chances of drug leakage and NLCs is therefore a more dependable platform in drugs that need to be released over a long period and have stability in storage. Higher bioavailability, structural stability, and targeted drug release have made NLCs a promising and versatile platform to deliver poorly soluble drugs in a nature that ensures its therapeutic efficacy in longer periods[18].

c. Self-Emulsifying Drug Delivery Systems (SEDDS)

SEDDS represents a high-tech lipid-based system of oils, surfactants and co-surfactants that form fine oil-in-water emulsions spontaneously when in contact with the gastrointestinal fluids. Such special self-emulsifying characteristic increases the dissolution and absorption of hydrophobic drugs by beating the difficulties of low water solubility. Cyclosporine preparations in SEDDS formulation showed a much better systemic exposure and lymphatic distribution in dog models. SEDDS may substantially bypass first-pass metabolism, thereby enhancing bioavailability and more predictable therapeutic plasma concentrations, and have a specific advantage with drugs subject to hepatic degradation[19].

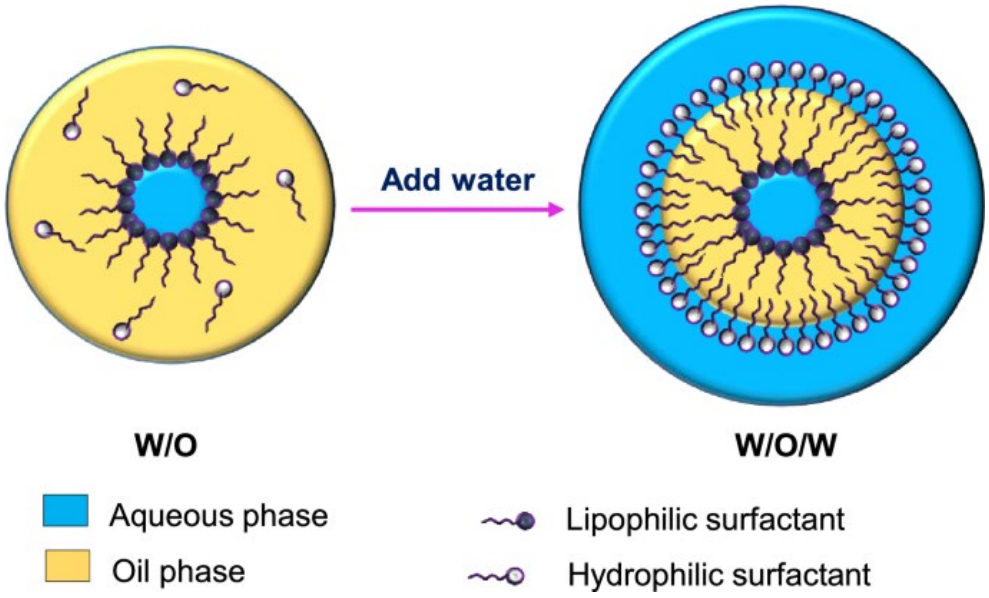

Figure 4: SEDDS[20]

In spite of these strengths, there are also limitations on the use of SEDDS that need to be overcome in order to use it in clinical practice. Surveys of these high concentrations of surfactants and co-surfactants needed to sustain effective emulsification may occasionally result in gastrointestinal irritation or toxicity particularly in long-term or high dosage[21]. Thus, optimization of formulation (e.g. choice of biocompatible excipients) is very important to guarantee safety, tolerability, and effectiveness. Well-constructed SEDDS can therefore be a valid approach in enhancing poor oral delivery of poorly soluble drugs coupled with reduced adverse effects.

4. ANIMAL-BASED INSIGHTS ON LIPID NANOCARRIERS FOR ORAL DRUG DELIVERY

Animal experiments have played a significant role in assessing the effectiveness and drug pharmacokinetic performance of lipid nanocarriers (LNCs) in the oral delivery of poorly soluble drugs. Rat and mouse rodent models have been widely availed as initial screening devices since they are relatively inexpensive, simple to handle and can be well-characterized physiologically. These researches are important considering the critical information on the role of LNCs in drug absorption, bioavailability, and blood circulation[22]. As an example, rats fed on oral curcumin-loaded solid lipid nanoparticles (SLNs) had a much high plasma concentration and bioavailability of the curcumin suspension in comparison with the traditional curcumin suspension. The main reason behind such improvements is the capacity of the lipid matrix to increase drug solubilization in the gastrointestinal tract, in addition to safeguarding labile compounds against enzymatic breakdown[23].

In addition to rodents, other models have involved dogs, which are bigger animals in order to study lipid-based preparations targeting lymphatic transport. Cyanosporine in self-emulsifying drug delivery systems (SEDDS) administered to dogs orally demonstrated improvement on lymphatic uptake and systemic exposure[24]. This finding highlights the possibilities of lipid nanocarriers to avoid the first-pass metabolism which is usually the disadvantage of using oral drug delivery,

which lowers the concentration of drugs in the body. The increase in lymphatic absorption does not only lead to a better bioavailability but also provides prospects with the administration of drugs with narrow therapeutic index or those which are heavily processed by the liver[25].

Besides enhanced absorption, animal research has also brought out the distribution and circulation of the drugs using LNCs. NLCs made of solid and liquid lipids have been demonstrated to extend the circulation period and enhance tissue-specific delivery in mice. As an illustration, loading quercetin into NLCs resulted in better accumulation of the target organs and increased antioxidant action, which implies that the lipid matrix does not only enable absorption, it also regulates pharmacodynamics. These results suggest the flexibility of LNCs to maximize therapeutic efficacy as well as tissue targeting[26].

Nonetheless, animal research also demonstrates that there are certain limitations and challenges of lipid nanocarriers. Polymorphic transitions, leaking the drug, or aggregation during storage may impair its formulation stability, potentially affecting reproducibility and predictability in vivo. In addition, although rodent and canine models offer meaningful data, the extrapolation of the results to human beings is a complicated matter because interspecies variations in the gastrointestinal physiology, enzyme activity, and lipid absorption pathways may affect pharmacokinetics[27]. So, in spite of the fact that animal-based research represents a good background of LNCs development, special attention and additional confirmation in human clinical studies is highly needed.

Table 1: Summary of Key Studies on Lipid-Based Nanocarriers for Drug and Nutraceutical Delivery[28]

Author(s) & Year	Focus Area	Methodology	Key Findings
Ranjbar et al. (2023)[29]	Liposomes, nanoemulsions, and SLNs for flavonoid delivery	Review of various lipid-based carriers	Lipid-based carriers enhanced solubility, stability, and bioavailability. Liposomes efficiently encapsulated hydrophilic and lipophilic compounds, while nanoemulsions and SLNs improved absorption and provided sustained release.
Rehman et al. (2024)[30]	SLNs, NLCs, and self-emulsifying systems for poorly soluble drugs	Literature review of lipid-based nanoformulations	These carriers improved pharmacokinetics and bioavailability, facilitated lymphatic transport, bypassed first-pass metabolism, and allowed controlled drug release, enhancing oral drug delivery.

Samimi et al. (2019)[31]	Characterization and biological interactions of lipid nanoparticles	Review and analysis of lipid nanoparticle properties	Particle size, surface charge, and lipid composition were critical for pharmacokinetics and biodistribution. Lipid-based carriers improved solubility, stability, and therapeutic efficacy of hydrophobic drugs.
Shirodkar et al. (2019)[32]	SLNs and NLCs for oral bioavailability enhancement	Review of formulation strategies and performance	SLNs provided sustained release and gastrointestinal protection; NLCs enhanced drug loading, minimized drug expulsion, and improved stability, supporting oral bioavailability of poorly soluble drugs.
Subramanian (2021)[33]	SLNs and NLCs for nutraceutical compounds	Review of lipid-based nutraceutical formulations	SLNs and NLCs improved solubility, absorption, and stability of nutraceuticals, facilitated prolonged circulation and targeted delivery, enhancing therapeutic efficacy.
Swarnakar et al. (2018)[34]	Critical parameters for oral delivery performance	Comprehensive review of in vitro characterization methods	Particle size, polydispersity index, zeta potential, drug encapsulation efficiency, and in vitro release profiles were crucial for predicting in vivo performance, ensuring reproducibility, stability, and efficacy of lipid-based drug delivery systems.

5. DISCUSSION

LNCs have become one of the most promising methods of the enhancement of oral drug delivery of poorly soluble drugs. The reviewed preclinical and animal-based studies prove that SLNs, NLCs, and SEDDS can substantially improve the drug solubility, absorption, bioavailability, and systemic distribution[35]. The mechanisms through which these improvements occur are mainly encapsulation of lipid matrices, gastrointestinal protection, sustained release and lymphatic transport, which avoids first-pass metabolism. Taken together, these results highlight the opportunity of lipid nanocarriers to address some of the major shortcomings of traditional oral preparations of hydrophobic drugs.

a. Interpretation and Analysis of Findings

As the evaluated evidence shows, SLNs can be used in improving oral absorption of hydrophobic drugs to allow a solid lipid matrix that delivers them after a prolonged period and protects them against the gastrointestinal tract. Nevertheless, issues like polymorphic transitions and drugs expelling in storage can reduce their stability over the long-term[36]. Having fused solid and liquid lipid, NLCs are more advantageous in loading drugs, minimized leakage, and enhanced tissue penetration, thus they are superior over SLNs in respect to stability and pharmacokinetics. They have special properties of lymphatic delivery, increase systemic exposure, and avoid first-pass metabolism, but SEDDS must be developed with caution to prevent gastrointestinal irritation by the presence of surfactants. On the whole, these studies are able to confirm that lipid nanocarriers have the potential to increase oral bioavailability and pharmacodynamic performance of insoluble drugs and point to formulation-specific benefits and drawbacks[37].

b. Implications and Significance

These findings bear implications on medication development as well as clinical therapeutics. LNCs have the potential to minimize dose to be used by patients, improve patient compliance, and minimize side effects caused by traditional oral preparations by enhancing solubility and systemic exposure[38]. The capability to adjust the pharmacokinetics and tissue distribution also creates opportunities of targeted therapy, extended activity of drugs, and treatment of drugs with a limited therapeutic index by LNCs. Formulation wise, these systems have provided scalable systems of these hydrophobic drugs which would otherwise have had difficulties in absorption and stability.

c. Gaps and Future Research Directions

Even though the results are promising, there are a number of gaps. The gastrointestinal physiology of animal models and human beings differs, which creates challenges in translating results to humans and thus restricts their predictability[39]. The optimization of lipid nanocarriers in terms of long-term stability, reproducibility, and large-scale production is necessary. Also, the pharmacokinetic characteristics of excipients, especially surfactants in SEDDS, should undergo a thorough assessment in the case of chronic use. In future studies, it should be done:

1. Carrying out human clinical trials to ensure preclinical discovery.
2. Coming up with standardized, scalable and reproducible LNC formulations.
3. Investigation of more advanced targeting methods and stimuli selective lipid carriers.
4. Exploring combination therapies and multi-drug delivery with the help of LNCs in order to achieve the greatest therapeutic effects.

Through these gaps, lipid nanocarriers would be efficiently scaled up to clinical settings out of preclinical models with robust solutions to oral delivery of poorly soluble therapeutics[40].

6. CONCLUSION

Lipid-based nanoparticles (LNCs) are one of the most promising approaches to improving the absorption of poorly dissolvable drugs through the mouth. These systems have been shown to significantly enhance drug solubility, absorption, bioavailability and systemic distribution in

preclinical and animal-based investigations due to different mechanisms including encapsulation in lipid matrices, gastrointestinal degradation protection, sustained release and lymphatic bypass of the first-pass metabolism. Though SLNs offer sustained release and gastrointestinal protection, NLCs offer greater drug loading, stability and release control, and SEDDS offer greater lymphatic uptake and systemic exposure. Although these benefits are evident, some issues such as stability of formulation, mass production and interspecies transcription are still there, which makes it necessary to further optimize and provide clinical validation. On the whole, LNCs offer a flexible and promising material to create patient-friendly efficacious oral formulations of hydrophobic drugs and the potential to achieve clinical translation and therapeutic use in the future is enormous.

CONFLICT OF INTEREST

The authors have no conflicts of interest regarding this investigation**.**

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