IJARSCT
International Journal of Advanced Research in Science, Communication and Technology
International Open-Access, Double-Blind, Peer-Reviewed, Refereed, Multidisciplinary Online Journal
ISSN: 2581-9429
Volume 5, Issue 2, December 2025
Impact Factor: 7.67

A Review Oflipid-Based Drug Delivery System: Advances in Oral Application

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Abstract: *Lipid-based drug delivery systems (LBDDS) have emerged as a highly effective approach for improving the solubility, permeability, and oral bioavailability of poorly water-soluble drugs. These systems—comprising lipid solutions, emulsions, self-emulsifying systems, solid lipid nanoparticles (SLN), and nanostructured lipid carriers (NLC)—utilize physiological lipid digestion pathways to enhance drug solubilization and absorption. LBDDS facilitate increased gastrointestinal residence time, lymphatic transport, efflux inhibition, and reduced first-pass metabolism, making them particularly advantageous for oral delivery. Advances in nanotechnology and excipient design have further improved the stability, targeting efficiency, and therapeutic performance of lipid-based formulations. Despite challenges related to formulation complexity, scalability, and stability, LBDDS have demonstrated substantial promise in overcoming barriers associated with conventional drug delivery. This review highlights the mechanisms, classification systems, formulation strategies, and applications of LBDDS, emphasizing their role as a versatile and innovative platform for enhancing the therapeutic outcomes of modern pharmaceuticals.*

Keywords: Lipid-based drug delivery system (LBDDS); Oral drug delivery; Bioavailability enhancement; Poorly water-soluble drugs; Solid lipid nanoparticles (SLN); Nanostructured lipid carriers (NLC); Self-emulsifying drug delivery systems (SEDDS); Self-microemulsifying drug delivery systems (SMEDDS); Lipid formulation classification system (LFCS)

I. INTRODUCTION

A novel drug delivery system is a new approach that utilises new technologies, innovative ideas, and methodologies to deliver the active molecules in a safe yet effective concentration to produce the desired pharmacological action. It is a formulation or device that delivers a drug to a specific site in the body at a specific rate.Drug delivery: A drug delivery system (DDS) is defined as a formulation or a device that enables the introduction of a therapeutic substance into the body and improves its efficacy and safety by controlling the rate, time, and place of release of drugs in the body. This process includes the administration of the therapeutic product, the release of the active ingredients by the product, and the subsequent transport of the active ingredients across the biological membranes to the site of action.[1]

Lipid-based drug delivery system: The field of drug delivery has seen remarkable advancements over the years, with the primary objective of maximizing therapeutic efficacy while minimizing adverse effects. Among the various delivery systems explored, Lipid-Based Drug Delivery Systems (LBDDS) have emerged as a potential approach to improve the bioavailability of drugs. Bioavailability, the fraction of an administered dose that reaches the systemic circulation, is a critical factor in the effectiveness of pharmaceutical agents. This article explores the mechanisms, benefits, and challenges of lipid-based drug delivery systems in enhancing bioavailability.[2]

DOI: 10.48175/IJARSCT-30342

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Advantages of a lipid-based drug delivery system

- Drug release in a controlled and targeted way.
- Pharmaceutical stability.
- High and enhanced drug content (compared to other carriers).
- Feasibility of carrying both lipophilic and hydrophilic drugs.
- Biodegradable and biocompatible.
- Excipients versatility.
- Formulation versatility.
- Low risk profile.
- Passive, non-invasive formation of the vesicular system, which is available for immediate commercialisation.[3]

In oral application:

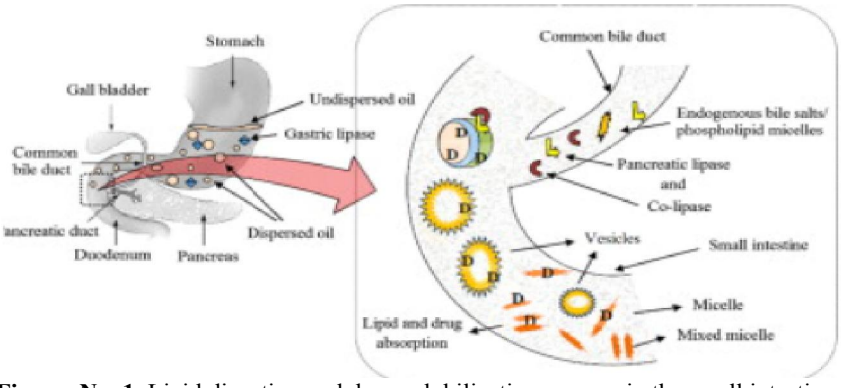

Figure. No. 1. Lipid digestion and drug solubilization process in the small intestine [4]

Amongst all delivery routes, oral delivery is the patient-friendly and prime choice for drug administration in clinical settings. LBDDS may enhance oral drug delivery by improving multiple mechanical pathways, such as extending gastric residence time, facilitating intestinal to lymphatic transport, enhancing intestinal epithelium permeability with reduced efflux transporter activity, and mitigating metabolic properties.[5]

Lipids may improve the oral bioavailability of poorly water-soluble drugs by a number of possible mechanisms. Lipids can increase effective drug solubility in the GI tract and blood vessels, e.g., the presence of lipids in the GI tract stimulates the secretion of bile salts and endogenous biliary lipids, such as phospholipids and cholesterol, forming intestinal mixed micelles, and then increases the solubilization capacity of the GI tract. Moreover, as a result of the intercalation of administered lipids into these bile salt structures, either directly or by secondary digestion, Lipids cause the swelling of micellar structures and a further increase in solubilization capacity.[6] Lipids can also increase the gastric retention time, resulting in slow delivery to the absorption site and increasing the time available for absorption. Even though passive intestinal permeability is not considered to be a major limitation to the bioavailability of most poorly water-soluble drugs, various combinations oflipids, lipid digestion products, and surfactants have been shown to have permeability-enhancing properties.[7]

LIPID-BASED DRUG DELIVERY SYSTEM

Advances in pharmaceutical research are focused on new delivery systems utilising new devices to achieve modification of delivery time, targeting, as well as improving the *in vivo* solubility and hence bioavailability of poorly soluble drugs. Lipid-based drug delivery systems (LDDS) consist of a diverse group of formulations, each consisting of varying functional and structural properties that are amenable to modifications achieved by varying the composition of lipid excipients and other additives. LDDS has evolved, over time, from micro- to nanoscale, enhancing the efficacy and therapeutic application of these systems. LDDS are accepted, proven commercially viable strategies for formulating

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challenging pharmaceutical molecules and can be tailored to meet a wide range of product requirements. Generally, most lipid drug delivery systems used as drug carriers have high stability, high carrier capacity, the feasibility of incorporating both hydrophilic and hydrophobic substances, and the feasibility of variable routes of administration, including oral, topical, parenteral, and pulmonary routes. LDDS can also be designed to allow modified drug release from matrices. LDDS could be broadly grouped into four: solid lipid particulate dosage forms, emulsion-based systems, solid lipid tablets, and vesicular systems. Modifications from these four types include: lipospheres, solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLC), lipid drug conjugate nanoparticles (LDC), self-emulsifying formulations (SEFs), Pickering emulsions, dry emulsions, micro and nano-emulsions, solidified reverse micellar solution (SRMS) based tablets, liposomes, herbosomes, cryptosomes, and transferosomes, amongst others. This work exhaustively reviewed the advances in LDDS and also drew comparisons between the different types based on history, methods of manufacture, applications, advantages, and disadvantages.[8]

LIPID-BASED DRUG DELIVERY FORMULATION:

Formulation type	Materials	Characteristics
Type I	Oils without surfactants (e.g. tri-, di-and monoglycerides)	Non-dispersing, requires digestion
Type II	Oils and water-insoluble surfactants	SEDDS formed without water-soluble components
Type III	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water-soluble components
Type IV	Water-soluble surfactants and colsolvents (no oils)	Formulation disperses typically to form a micellar solution

Table No. 01 Formulation Types and their material with classification.[9]

The Lipid Formulation Classification System (LFCS) was introduced as a working model in 2000, and an extra 'type 'of formulation was added in 2006. In recent years, the LFCS has been discussed more widely within the pharmaceutical industry to seek a consensus that can be adopted as a framework for comparing the performance of lipid-based formulations.[10]Lipid-based formulations have been used for the oral administration of drugs that are poorly soluble in water, such as BCS classes II and IV drugs. Such formulations represent 3% of the total drug products available in the market (Hauss, 2013). Depending on their composition, size, and chemical characteristics, lipid-based systems can be further classified into lipid solutions, lipid suspensions, emulsions, multiple emulsions, micro- and nanoemulsions, self-emulsifying and self-microemulsifying systems, solid lipid nanoparticles, solid lipid dispersions, noisome, and liposomes.The digestion of lipids is started in the stomach by gastric lipases. Shear forces in the digestive tract and stomach emptying assist in the emulsification of the drug before emptying into the duodenum. Secretion of pancreatic enzyme lipase, together with its co-factor colipase, facilitates the breakdown of ingested glycerides to diglycerides,monoglycerides, and fatty acids. The existence of fatty diets in the intestine also stimulates the gallbladder biliary secretions of bile salt, cholesterol, and phospholipids.[11]

ROLE OF LIPID IN BIOAVAILABILITY ENHANCEMENT

The bioavailability of some of the drugs is increased when co-administered with food. However, many drug molecules have negligible interaction with food. BCS class I drugs are not affected by the presence or absence of food, but class II drugs have an altered absorption when co-administered with food. There is a on that such enhanced bioavailability might be attributed to solubility, permeability, and inhibition of efflux transporters in the presence of food. Some of the drugs which show enhanced bioavailability when administered along with food are griseofulvin, halofantrine6, danazol 5, troglitazone, and atovaquone. A guidance document entitled "Food-Effect Bioavailability and Feddie-Bioequivalence" was issued by the FDA in December 2002. The USFDA recommended high-fat meals for food-effect studies because such fatty meals (800–1000 cal,50%–65% fat,25%–30% carbohydrates, and15%–20% proteins) affect GI physiology and maximise drug transfer into the systemic circulation. In particular, it is the lipid component of the

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food that plays a vital role in the absorption of lipophilic drugs, leading to enhanced oral bioavailability. This can be explained by the ability of a high-fat meal to stimulate biliary and pancreatic secretions, to decrease metabolism and efflux activity, to increase intestinal wall permeability, and to a gastrointestinal (GIT) residence time and transport via the lymphatic system. Triglycerides and the GIT residence time. Also, a high-fat diet elevates the TG-rich lipoproteins, which react with drug molecules. This association of lipoproteins with drug molecules enhances intestinal lymphatic transport and leads to changes in drug disposition and finally changes the kinetics of the pharmacological actions of poorly soluble drugs. This food effect on drug absorption leads to a serious concern about the sub-therapeutic plasma drug concentration when co-administered without food. Such a food effect is also a serious problem for drugs with a narrow therapeutic index, where increased bioavailability may lead to serious untoward effects. Hence, controlling/monitoring the dosing of such drugs. However, food-dependent bioavailability can be significantly reduced by formulating the drug as a lipid-based formulation, which can increase the solubility and dissolution of lipophilic drugs and facilitate the formation of solubilised species, from which absorption occurs. Hence, lipid-based formulations can be used to reduce the dose of the drug while simultaneously enhancing its oral bioavailability.[12]

LIPID FOR DRUG DELIVERY APPLICATION

For drug delivery formulation, lipids as drug delivery vehicles need to be chosen carefully. For oral drug administration, lipids can be divided roughly into digestible and nondigestible in the GI tract.[13]

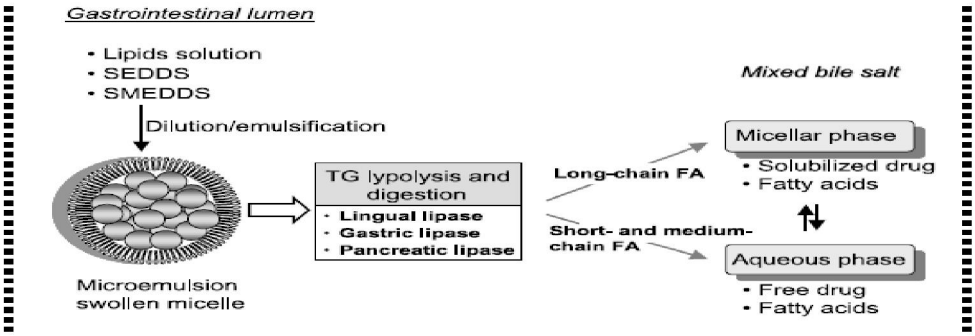

Figure no.02. Schematic diagram of the in vivo lipid digestion process from lipid-based formulations. SEDDS, self-emulsifying drug delivery systems; SMEDDS, self-emulsifying microemulsion drug delivery systems; TG, triglyceride; FA, fatty acid. (Adapted from Myers and Stella).[14]

The digestible lipids are composed of dietary lipids such as glycerides, fatty acids, phospholipids, cholesterol, and cholesterol esters, as well as various synthetic derivatives, e.g., triglyceride lipids can be digested or hydrolysed into diglycerides and fatty acids by the lingual and gastric lipases in the stomach.[15] The pancreatic lipase hydrolyses the triglyceride lipids further, producing 2-monoglyceride and two fatty acids. The presence of the hydrolysed products induces secretion of biliary and pancreatic fluids, causing a substantial change in the luminal environment. Moreover, the digested products are more water-soluble than the parent lipids, and they can be solubilised within bile salt mixed micelles. Figure no.02. On the other hand, nondigestible lipids include mineral oil (liquid paraffin) and sucrose polyesters. When administered, they remain in the lumen and can decrease drug absorption by holding a fraction of the co-administered drug.[16] Lipids can also be classified depending on raw materials (plant or animal), sources (natural, synthetic, or semi-synthetic), physical states (solid, semisolid, or liquid), polarity (polar or nonpolar), and molecular structures (triglycerides, hydrocarbons, or polyalcohol's). Generally, it is not so easy to tell which lipid can enhance the bioavailability of poorly water-soluble drugs, and this depends on each formulation. For example, e.g. when examining the effects of digestible and nondigestible lipids on the bioavailability of poorly soluble drugs (acetyl Sulfisoxazole and griseofulvin) in rats, the bioavailability of griseofulvin decreased in all lipids.[17] However, in the case of acetyl sulfisoxazole, when digestible lipids were used, bioavailability increased, unlike with nondigestible lipids. Moreover, the maximum serum concentration level of the medium-chain triglyceride formulation was fourfold higher than that of the nondigestible formulation.[18]

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FACTORS TO BE CONSIDERED IN DESIGNING LIPID-BASED FORMULATION:[19]

- Capacity of the solvent,
- properties of lipid excipients,
- lipophilicity of surfactant excipients,
- digestion in the GIT, and
- solvent miscibility.

FORMULATION CONSIDERATION

Preliminary studies are performed for the selection of oil, which is an important and critical requisite for the formulation of SEDDS and SMEDDS/SNEDDS. The solubility of a drug is determined in various oils and surfactants. Prepare a series of delivery systems containing the drug in various oils and surfactants. Then, in vitro self-emulsification properties and droplet size analysis of these formulations upon their addition to water under mild agitation conditions are studied. A pseudo-ternary phase diagram is constructed, identifying the 99.50% efficient self-emulsification region. The use of lipid excipients for formulations is inevitably complicated and thus has presented challenges to both pharmaceutical and regulatory scientists. Lipid excipients can solubilise hydrophobic drugs within the dosage form matrix. However, as with dietary lipids, these excipients can also be digested and dispersed in the GI tract. Therefore, one of the questions for a lipid-based oral formulation is whether the drug remains in solubilised form in the presence of changing phases of the formulation after it is administered. This is a difficult question, which can be illustrated b simplified phase diagram for an oily formulation dispersed in water and a surfactant. As shown in Fig. no.03, various possible lipid assemblies can arise from the interplay of the three major components (i.e., oil, water surfactant) present in the system.[20] These assemblies may include emulsion, micelle, water-in-oil microemulsion, oil-in-water microemulsion, and BI continuous microemulsion. The phase of the lipid formulation may be changing as it reaches the GI tract and is subject to the digestion, dispersion and transport process in the body.[21]

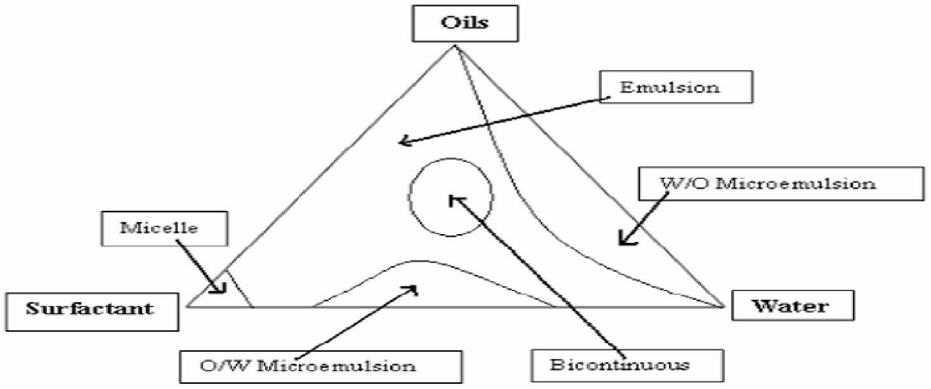

Figure no. 03. A simplified phase diagram for an oily formulation dispersed in water and a surfactant.[22]

II. CONCLUSION

Lipid-based drug delivery systems (LBDDS) have emerged as a promising strategy to enhance the solubility, stability, and bioavailability of poorly water-soluble drugs, particularly in oral applications. By utilising lipid excipients and nanostructured carriers such as solid lipid nanoparticles, nanostructured lipid carriers, and self-emulsifying systems, these formulations enable improved drug absorption through mechanisms like enhanced solubilization, lymphatic transport, and efflux inhibition.

LBDDS not only improve therapeutic efficacy but also offers controlled release, reduced toxicity, and better patient compliance. However, formulation challenges such as stability issues, complex manufacturing processes, and inter-individual gastrointestinal variability remain to be optimised.

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Overall, LBDDS represent a significant advancement in modern pharmaceutics, providing a versatile and effective platform for delivering challenging drug molecules. Continued research and innovation in lipid excipient design, nanotechnology, and biopharmaceutical evaluation will further strengthen their role in achieving enhanced oral bioavailability and targeted therapeutic outcomes.

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