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Review

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Exploring LIPID's for their Potential to Improves bioavailability of lipophilic drugs candidates: A REVIEW

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ABSTRACT

This review aims to provide a thorough examination of the benefits, challenges, and advancements in utilizing lipids for more effective drug delivery, ultimately contributing to the development of innovative approaches in pharmaceutical science. Lipophilic drugs, characterized by low aqueous solubility, present a formidable challenge in achieving effective delivery and absorption within the human body. To address this issue, one promising approach involves harnessing the potential of lipids. Lipids, in their diverse forms, serve as carriers, leveraging their unique capacity to enhance solubility, stability, and absorption of these challenging drugs. By facilitating improved intestinal solubility and selective lymphatic absorption of porously permeable drugs, lipids offer an array of possibilities for drug delivery. This versatile characteristic not only bolsters the pharmacological efficacy of drugs with low bioavailability but also contributes to enhanced therapeutic performance, ultimately reducing the required dose size and associated costs. This comprehensive review delves into the strategic formulation approaches that employ lipids as carriers to ameliorate drug solubility and bioavailability. Emphasis is placed on the critical considerations of lipid type, composition, and processing techniques when designing lipid-based formulations. This review meticulously examines the multifaceted challenges that come hand in hand with lipid-based formulations for lipophilic drugs, offering an insightful perspective on future trends. Regulatory considerations and the broad spectrum of potential applications are also thoughtfully discussed. In summary, this review presents a valuable repository of insights into the effective utilization of lipids as carriers, all aimed at elevating the bioavailability of lipophilic drugs.

Keywords: Lipids, lipophilic drugs, bioavailability, lipid-based nanoparticles, liposomes, self-emulsifying drug delivery systems, lipid-based micelles, solubility, stability, drug absorption, formulation approaches.

Abbreviation:

LBF: Lipid based formulation; FA: Fatty Acid; BS: Bile Salt; IVIVC: In-vitro-In-vivo correlation; TGs: Triglycerides; TRL: TG's-rich lipoproteins; FDA: Food and Drug Administration; BCS: Biopharmaceutical Classification System; MGs: Monoglycerides; ER: Endoplasmic reticulum; FDA: Lipophilic drugs; SEDDS: Self-emulsifying Drug Delivery Systems; LCT: Long chain triglycerides; MCT: Medium chain triglycerides; SMEDDS: Self-Microemulsifying Drug Delivery Systems; CYP: cytochrome P450; CYP3A4: Cytochrome 450 3A4; FFA: Free fatty acids; CMC: Critical micelles concentration; LFCS: lipid formulation classification system; MLV: multilamellar vesicles; SUV: unilamellar vesicles; LUV: large

unilamellar vesicles; SLN: Solid- Lipid Nanoparticles; P-gp: P-Glycoprotein; API: Active Pharmaceutical Ingredient; SI: Small Intestine; FA: Fatty Acid; BS: Bile Salt; PUFA: Polyunsaturated Fatty Acid; HPMC: Hydroxy-Propyl Methyl Cellulose; HLB: Hydrophilic-Lipophilic Balance; SCF: Supercritical Fluid; DLS: Dynamic Light Scattering; EM: Electron Microscopy; SEM: Scanning Electron Microscopy; TEM: Transmission Electron Microscopy; AFM: Atomic Force Microscopy; ELS: Electrophoretic Light Scattering; HPLC: High-Performance Liquid Chromatography; DSC: Differential Scanning Calorimetry; XRD: X-ray Diffraction; NMR: Nuclear Magnetic Resonance; NLC: Nanostructured Lipid Carriers; ADME: Absorption, distribution, metabolism, and excretion; Cmax: maximum plasma concentration; Tmax: Time to reach maximum plasma concentration; AUC: area under the curve; t1/2: elimination half-life; PET: positron emission tomography; SPECT: single-photon emission computed tomography; USP: United States Pharmacopeia; NF: National Formulary; EP: European Pharmacopoeia; USFA: Unsaturated Fatty Acids; USA-NF: United States Pharmacopeia in combination with National Formulary; USA/FA: United States Pharmacopeia/National Formulary; FCC: Food chemical codex; JSFA: Journal of the Science of Food and Agriculture; JPED: Japanese Pharmaceutical Excipients Directory; IIG: Inactive Ingredient Guide; JCIC: Japanese Cosmetic Ingredients Codex; LBODDS: Lipid Based Oral Drug Delivery System; GI: Gastrointestinal; GIT: Gastrointestinal Tract; CL: Cholesterol; PL: Phosphotidylcholine; SI: Small Intestine

1. Introduction

In the current scenario, the delivery of oral drugs is continuously considering for novel possibilities due to the understanding, that influences for instance poor drug dissolution, poor permeation through biological membrane, drugs first-pass metabolism, variations in the drug bioavailability, as well as influence food, are important contributors to the standard dosage form's failure due to unsatisfactory *In-vivo* outcomes (Pandey and Kohli, 2018). With the growing popularity of lipids as a carrier for hydrophobic medicines delivery since the start of the 20th century, drug administration *via* the oral route has taken on an entirely novel aspect. (Pouton, 2006).

Lipids' distinct qualities, such as their biocompatibility, physiochemical variation, and demonstrated potential to enhance hydrophobic medications' oral route bioavailability via preferential the lymphatic absorption, rendering lipids especially appealing as bearers for oral formulations. Lipid-based oral drug delivery systems (LBODDS) are gaining attention due to their promising potential (Chakraborty et al, 2009; Porter et al, 2001; Pouton and Porter 2008; Trevaskis, 2008; Brogård et al., 2007). There are several factors can influence drug bioavailability, and they interact with lipids in the digestive process in various ways. The physicochemical properties of a drug, such as solubility, particle size, and ionization, can impact its absorption. Lipid-based formulations are designed to address the challenge of poor solubility

by enhancing the drug's solubility in lipids, making it more bioavailable. Gastrointestinal pH levels play a crucial role in drug solubility and absorption, and lipids can protect drugs from degradation in the acidic stomach environment. Enzymes in the gastrointestinal tract can metabolize and inactivate drugs, but lipid-based formulations can act as protective barriers, shielding the drugs from enzymatic degradation and improving absorption. The presence of food can affect drug solubility, especially for lipid-based formulations, as they may require specific conditions for optimal drug release and absorption, which can vary with food intake. The design of lipid-based formulations (LBF), including the type of lipids and surfactants used, plays a vital role in drug solubility and bioavailability. These formulations are customized to address specific drug and gastrointestinal challenges, making them a versatile approach to improving drug bioavailability and therapeutic effectiveness.

The challenges related to lipid-based drug delivery systems include: A) Lipid-based systems can be complex due to the various types of lipids used, making formulation and understanding these systems challenging. B) Maintaining the stability of lipid-based products during manufacturing and storage can be difficult, impacting their commercial viability. C) Lipids may not improve the solubility of all hydrophobic drugs, limiting their effectiveness. D) Understanding how these systems interact with the gut before drug absorption can be a complex area of study. F) There is a dearth of information on how drug-lipid interactions occur in the human body, making it challenging to predict real-world outcomes. G) The absence of reliable procedures for correlating *In-vitro* (laboratory) results with *In-vivo* (in the body) outcomes complicates the development and testing of lipid-based drug delivery systems. These challenges reflect the intricate nature of developing and utilizing lipid-based drug delivery systems and highlight areas of research and development in this field (Silva et al., 2022). LBFs have shown great promise in various therapeutic areas and with a wide range of drugs. In oncology, for instance, LBFs have been used to enhance the delivery of chemotherapeutic agents, such as paclitaxel (Alavi and Nokhodchi 2022), improving their therapeutic effectiveness. In antifungal therapy, LBFs have been employed to improve the solubility and bioavailability of drugs like Amphotericin B (Faustino and Pinheiro, 2020). These formulations have also demonstrated promise in antiretroviral drugs like saquinavir (Hosny et al 2023) more bioavailable. Additionally, lipid-based systems have been utilized to improve the delivery of immunosuppressants, like cyclosporine (Keohane et al., 2016), for organ transplant patients. The ability of LBFs to address the solubility and bioavailability challenges of a broad spectrum of drugs highlights their versatility and potential impact in various therapeutic areas (Pouton. 2000).

Several lipophilic drugs (anticancer drugs, antiretroviral drugs, etc.) are suitable for efflux transporters that include P-glycoprotein (P-gp) and are frequently susceptible to metabolism *via* cytochrome P450 (CYP) enzymes, resulting in significant first pass elimination (Chakraborty et al, 2009). These variables are sometimes the primary causes of hydrophobic drugs low oral bioavailability. As a result, there is a strong demand for an optimal nanocarrier system that considers all these factors and provide optimum delivery of lipophilic medications. In this context, nanocarriers made from lipids would be desirable formulation since they have the ability to solve these problems by enhancing and normalizing drug absorption (Chakraborty et al, 2009).

Formulation components that can be digestible in the Gastrointestinal tract (GIT) have a adequate influence in affecting the pharmacokinetic of drugs that is absorbed from the GIT

(Brogård et al., 2007). Researchers must have a thorough understanding of the Gastrointestinal (GI) digestive mechanism in order to assess the bio-pharmaceutical characteristics of LBF and to device suitable *In-vitro* studies to replicate the formulation's physical surroundings. Continual attempts are being made to design a bio-relevant dissolution medium need to comprehend the *In-vivo* colloidal behaviour of LBF under influence of inherent solvating aspects such as bile salts (BS), phosphotidylcholine (PL), and cholesterol (CL), as well as enzymes (lipase) (Narang et al., 2015).

This current assessment is an integrated tactic to comprehending the lipids role in both exogenously and endogenously for the enhancement of Biopharmaceutical classification system (BCS) II drug availability in systematic circulation, mechanisms associated with the process of digesting and transcellular transportation, formulation development challenges with a focus on solid dosage forms. The obstacles involved in formulation design, particularly solid dosage forms, as well as the progress made so far, in the creation of physically structural assessment of digestible lipidic yields, *In-vitro* lipid digestible design, *In-vivo* research, and *In-vitro-In-vivo* correlation (IVIVC).

2. Exogenous lipids' role in increasing drug systematic availability

The prerequisites for oral absorption include high solubility and permeability, and various medicines shown to have very poor and inconstant bioavailability because of greater dose-to-solubility ratio. Food co-administration typically increases the bioavailability of such medicines (Charman et al., 1997; Shah et al., 2014, 1995; Dressman et al., 1998). "**Crounse** was first person to explain the concept of food dependent systemic availability of medicinal products, showing that administration of a lipophilic griseofulvin, alongside a high-fat food significantly increased absorption **(**Crounse, Robert G 1961). The amount of fat in a meal significantly affects how the body absorbs lipophilic medicines. (Cunningham et al., 1991; Feinle et al., 2001; Stone et al., 1992; Froehlich et al., 1995).

A high-fat diet increases biliary and pancreatic secretions, which extends GIT residence time, increases lymphatic transportation, variations in mesenteric and hepatic systemic circulation, improves gastrointestinal membrane permeation, and decreases metabolic and efflux movement, all of that result in substantially higher bioavailability (Hoffman and Dahan, 2006, Wagner et al., 2001). In addition to well-known parameters (including bile salt and pH levels), research on healthy humans indicates that additional parameters such as osmosis, buffering ability, surface tension and meal constituents, that differ knowingly pre/postprandially, could affect the intraluminal effectiveness of delivery system (Kalantzi et al., 2006).

It has been demonstrated that eating meals comprising 10-25 g of fat promotes gallbladder emptying and utmost contraction in quantitative terms essential lipids in the diet is primarily triglycerides (TGs), which can exceed 100 g/day or additional in the intestine and long-chain (instead of medium-chain) FAs indicates to be of the greatest benefit in causing related to food restriction on motility, that could contribute to longer GI residence time (Stone et al., 1992; Froehlich et al., 1995, Mu, Huiling 2005; Fried et al., 1988, Raybould et al., 1998). Lymphatic absorption of specific lipophilic drugs or macromolecule can be augmented when a high-fat meal is present (Li, C et al., 2001; Martinez et al., 2002). According to **a** report alterations in the

disposition of drugs for some lipophilic substances could take place while the medicines reacts with TG's-rich lipoproteins (TRL), and the amount rises as an outcome of rich-fat meal intake (Gershkovich and Hoffman 2007). Perhaps it is the outcome of these intriguing findings that sparked the concept of a LBF for systemic availability improvements amongst modern scientists.

Exogenous lipids, often utilized in lipid-based drug delivery systems, play a crucial role in increasing the systemic availability of lipophilic drugs. By acting as carriers, they enhance drug solubility, stability, and absorption, thus addressing the challenges posed by poorly water-soluble drugs. This approach offers several advantages, including improved bioavailability, reduced inter- and intra-subject variability, and enhanced therapeutic outcomes. However, there are important drawbacks to consider. One key concern is the potential impact on overall caloric intake and nutritional balance, especially in cases of chronic drug administration. Additionally, the risk of lipid-induced gastrointestinal side effects, such as steatorrhea, may be heightened with prolonged use of lipid-based formulations (Natesan,et al., 2021) and the cost of production and potential challenges in achieving regulatory compliance are practical considerations that permit attention. Therefore, while exogenous lipids offer valuable solutions for drug delivery, a comprehensive risk-benefit analysis is crucial to balance the advantages with the potential drawbacks when considering their use in pharmaceutical formulations.

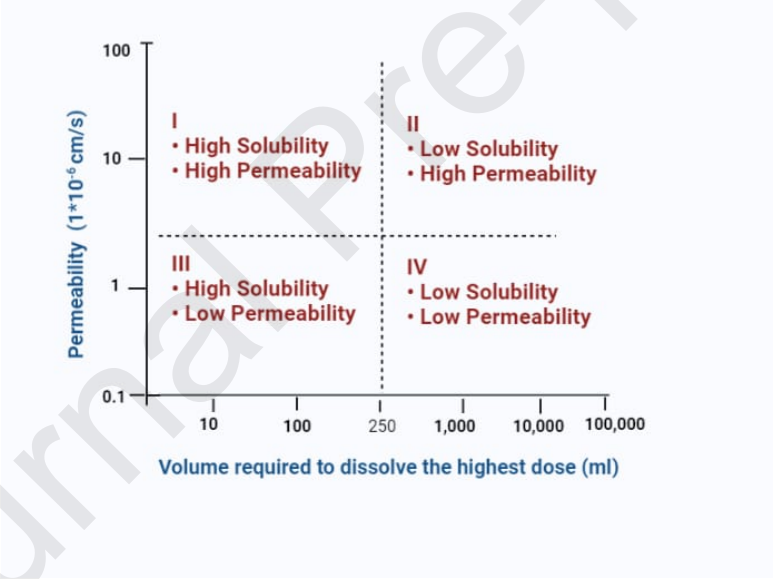


Figure: **1** Biopharmaceutical classification of drugs (Fleisher et al., 1999)

Several occurrences of food impacts on drug bio-availability have been documented in the literature in connection to drug class as defined by the BCS shown in **Figure 1**. It has been revealed that the bio-availability of Class I medications is unaffected by meals, whereas the bio-availability of Class II and III category drugs rises and falls, correspondingly. Solubility, permeation, and obstraction of efflux conveyer in occurrence of food can all be used to explain such data (Benet et al., 2003, 2004). Because of their great solubility and permeability, Class I medicines, can simply traverse the wall by passive absorption and have the capability of drenching any cell conveyer, including efflux and diffusion.

Because passive diffusion dominates the absorption process, transporters interaction with drug is low, and no significant impact on bio availability for Class I drugs is found in the existence of a rich-fat meal. In a comparable manner, because of its lipo-philicity and high permeability, Class II medicines are predominantly absorbed via passive diffusion. While, the poor solubility of these substances prevents efflux transporters from becoming saturated. As a result, the dual impact of inhibiting efflux transporters and increasing drug solubility in the presence of food enhances oral bio availability.

Class III drugs, while readily available in the lumen of the gut because of their high solubility, are poorly digested and absorptive, and hence rely heavily on cellular acceptance channels for entry into enterocyte (Fleisher et al., 1999; Custodio et al., 2008; Benet 2013). Drugs such as Esomeprazole may have decreased bio-availability with rich-fat food because of the blocking uptake transporters in the colon (Cheng and Wong 2020). Class III drugs are characterized by their low solubility and high permeability, and they often experience decreased bioavailability when administered with a rich-fat meal due to mechanisms involving uptake transporter blocking. These drugs are substrates for transporters like P-glycoprotein (P-gp) and organic anion transporting polypeptides (OATPs) that are essential for drug absorption. The high-fat content in a meal can lead to the release of bile salts, which are known inhibitors of OATPs. When OATPs are inhibited, it can result in reduced uptake of Class III drugs into enterocytes, ultimately lowering their bioavailability. Though Class IV drug are difficult to predict, they may act like Class III pharmaceuticals due to a rise in solubility in the existence of a meal that is rich in fat.

The interaction of subsequent TRL with water insoluble medicines in the enterocyte has been shown to be susceptible together colon lymphatic transit and post-absorptive variations in distribution and elimination of a drug after a meal with rich fat content. This medicine interaction reduces the volume of distribution and elimination, potentially changing the pharmaco-kinetics of the lipophilic drug's pharmacological activity (Gershkovich and Hoffman 2007). As a result, various hurdles arise in the formulation of drugs with dietary effects. When a rich-fat diet is essential to achieve efficient drug amount, here is substantial worry that patients taking the drug without meals will have sub-therapeutic drug concentrations in their plasma. Changes in bio-availability, especially rise, may cause undesired side effects with drugs of narrow therapeutic index. As a result, the treatment strategy may call for food intake regulator and/or observing in connection to dose. Though, the aforementioned problem may be solved through offering lipid-based delivery system. Despite the fact that the type and amount of lipids in a meal differ considerably from those in a medicinal product formulation, the construction of LBF can alleviate the fundamental disadvantages of deliberate and deficient dissolution of lipophilic drugs by encouraging the construction of dissolved phases where permeation may take place. This has the potential to improve their food-dependent permeability while simultaneously lowering the dose (Trevaskis et al., 2008). Grifofulvin (Aoyagi et al., 1982), Danazol (Charman et al., 1993), Halofantrine (Humberstone et al., 1996), Atovaquone (Nicolaides et al., 2000), and Troglitazone (Schmidt et al., 2002) are some drugs which shows increased bio-availability when administered with food.

Classification of lipids on the basis of their derived sources:

Lipids are fatty acids, their derived compounds, and molecules that are bio-chemically or functionally connected to these components (Christie and William, 1987) and their classification shown in **Figure 2**. The temperature at which it melts typically reduce with fatty acid unsaturation & elevates along with molecular weight (hydrocarbon chain length). The characteristics of lipids and surfactants, including their fatty acid compositions, solubility, melting temperatures, and hydrophilic-lipophilic balance (HLB), are pivotal factors in the formulation and efficacy of lipid-based pharmaceuticals. The choice of lipids influences the drug's solubility and stability within the formulation. The fatty acid composition and melting temperature determine the physical state of the lipid, impacting drug release rates. Surfactants, on the other hand, play a crucial role in emulsifying lipids and enhancing drug dispersion. The HLB of surfactants governs their ability to stabilize the formulation, improving drug bioavailability. Selecting the right combination of lipids and surfactants is essential for achieving the desired drug release profiles, stability, and absorption, ultimately influencing the therapeutic effectiveness of lipid-based pharmaceuticals. Lipids easy adoption in the formation of a system for oral administration is ascribed to

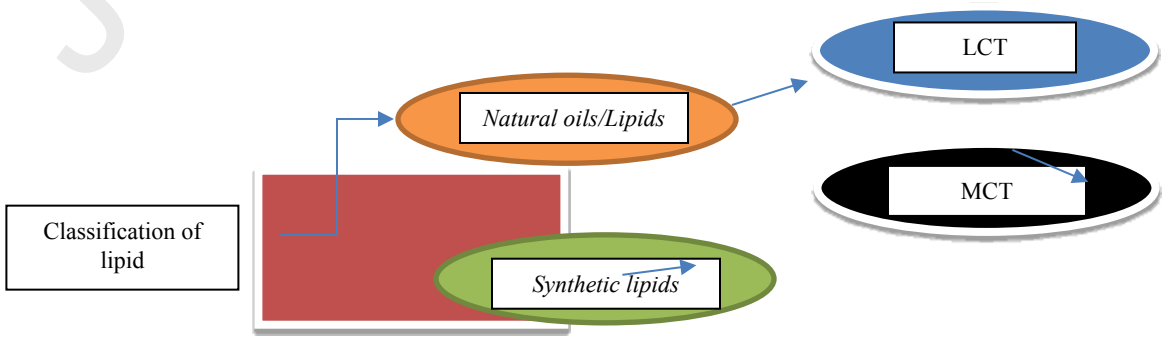
a.) Improve oral bioavailability & reduce plasma profile swings (Weng et al., 2014).

b.) Enhanced lipidic substance characterisation.

c.) Formulation versatility, as well as the capacity to choose from a number of pharmaceutical delivery methods

d.) The ease with which technology can be transferred and manufacturing scaled up (Qureshi et al., 2015, Carey 1983).

In the realm of drug delivery and bioavailability, there is a substantial body of research dedicated to both natural oils/lipids and synthetic/semi-synthetic lipids illustrated in **Figure 2.** Natural oils and lipids, derived from sources such as plant oils and animal fats, are often favored for their biocompatibility and safety. These lipids, including triglycerides and phospholipids, can be used to formulate lipid-based drug delivery systems, such as nanoemulsions, liposomes, and solid lipid nanoparticles. They play a crucial role in enhancing drug solubility and stability. In contrast, synthetic and semi-synthetic lipids, such as fatty acid derivatives and synthetic surfactants, offer precise control over lipid properties and can be tailored to address specific drug delivery challenges. These lipids provide versatility in designing drug carriers and can be engineered to achieve desired release kinetics.



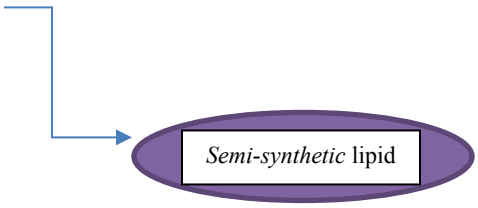


Figure: 2 Lipid Classification

a. Natural oils/Lipids (Long-Chain and Medium-Chain Triglycerides):

Plant-based oils that are treated & filtered to eliminate impurities or isolate distinct portions of the initial product have acquired interest in production of encapsulated oral formulation solutions. Natural oils/lipids are composed of triglyceride mixes including FA with unsaturation level & varying chain length. Melting point of a specified oil is inversely related to rising levels of unsaturation and directly proportionate to the fatty acid chain's length. The unsaturation level raises relative oxidation vulnerability. Triglycerides can be hydrogenated synthetically to reduce unsaturation and hence improve resistance to oxidative destruction. Natural oils are fractionated into individual glyceride portions in order to make excipients, which improves their physical & drug-absorption capabilities whereas minimising certain drawbacks, such as oxidation susceptibility (Carey 1983, Greenberger et al., 1966). Self-emulsifying drug delivery system (SEDDS) usually use triglyceride vegetable oils as a base. They are generally regarded as safe (GRAS) since they are common elements of foods all around the world. Long chain triglycerides (LCT), also known as long-chain unsaturated fatty acids, are a class of glyceride esters that are used to make vegetable oils. Number of oils made by using a wide range of botanical origins, & they contain varying quantities of fatty acids, as shown in **Table 1** Notably, saturated medium-chain oils, especially C12, are extremely abundant in fatty acid profiles of palm kernel & coconut oils. Medium chain triglycerides (MCT), also known as glyceryl tricaprylate/caprate, are a generic product that are produced by distilling coconut oil. It can be purchased from a wide variety of sellers and, in general, is made up of glyceryl esters in accumulation to a predominance of saturated C10 fatty acids (between 20 and 45 percent) and C8 fatty acids (between 50 and 80 percent). Because triglycerides have a high concentration of ester groups, which confer high solvent and lipophilicity ability for drugs, MCTs have a larger solvent capacity in comparison to LCTs on a weight basis (Anderson and Marra 1999; Cao et al., 2004)

Medium-chain triglycerides have several advantages which enable them ideal for lipid-based products: a.) MCT are easily absorbed, digested, & transported in disease whereas LCT absorption, transport & digestion are not ideal. b.) MCT are easily metabolized in body & have an extremely low tendency to turn into body fat. c.) MCT are a readily available and is a source of energy d.) MCT cause ketosis. e.) MCT are hydrogen ion donors & acetyl-CoA precursors. f.) In comparison to LCT (C12:0, C14:0, and C16:0), plasma levels of cholesterol are not increased by the presence of medium-chain triglycerides (Bach and Babayan 1982; Akula et al., 2014). While High doses of MCTs can lead to gastrointestinal side effects, including diarrhea, cramps, and stomach discomfort. Additionally, individuals with certain medical conditions, such as pancreatic issues or fat malabsorption disorders, may experience exacerbated symptoms with

MCT-containing formulations. Therefore, careful dosing and patient selection are crucial when incorporating MCTs into drug formulations to minimize the risk of adverse effects while maximizing the benefits of these lipid carriers.

a. *Synthetic and semi-synthetic lipids:*

Before combining them with other chemical substances, the production of these lipids involves adjusting the proportion of fatty acids or glycerides (mono-, di-, and tri-) present in a variety of naturally occurring liquid and semisolid excipients. This proportional heterogeneity is due to using diverse excipients now available in market for the production of oral lipid-based preparations (Hauss 2007). Prominent manufacturers like Abitech®, Gattefosse, Stepan®, and Sasol® provide a wide range of emulsifiers and solubilizers under various brands, & these formulations are primarily characterized by the amount of capric & caprylic acids. These excipients are utilised in the pharmaceutical industry as liquid thermoplastic semisolid solubilizing solvents, wetting agents, coemulsifiers and emulsifiers/surfactants in SEDDS, and self-micro emulsifying agents (SMEDDS). These excipients work well in hard gelatin capsule & soft gelatin capsules. They are capable of self-emulsifying and variation in HLB value from being extremely lipophilic (Pecol, having HLB 3.3) to being hydrophilic (Cremophore RH40, having HLB 14-16). The thermoplastic excipients, melt between 26 and 70°C & at room temperature found as a greasy semisolid substance, that are typically placed inside capsules in a molten form. Their application in firm gelatin capsules is constrained by excipient melting temperatures (Sharipova et al., 2014). In addition to contributing to increase the hydrophilicity of vegetable oils, certain procedures, such as polyglycolysis, interesterification, directesterification, and transesterification, also produce a range of partial triglycerides, monoglycerides, and polyoxyglycerides (Cho and Park 2014; Stella 2013). These are a well-known class of excipients which are used to enhance bioavailability & solubility of pharmaceuticals. There are several drugs that have effectively harnessed synthetic and semi-synthetic lipids in pharmaceutical formulations. For instance, AmBisome, a liposomal formulation of amphotericin B (Krishna, and Stipp, 2002), incorporates synthetic lipids and has improved drug solubility, reducing the nephrotoxicity commonly associated with this antifungal agent. The antisense oligonucleotide mipomersen, marketed as Kynamro, employs synthetic lipids to enhance drug stability and delivery, effectively treating familial hypercholesterolemia. Lomitapide, available as Juxtapid, is another example in the treatment of familial hypercholesterolemia, where synthetic lipids in the formulation optimize solubility and bioavailability (Weitz, 2014).). Moreover, Ibrutinib, used for treating certain cancers, leverages synthetic lipids in specific formulations to improve drug solubility and bioavailability, exemplifying the successful incorporation of synthetic and semi-synthetic lipids in pharmaceuticals. Table 2 summarizes the specifics of these excipients.

Table: 1 Fatty Acid Configuration in Oils of Botanical Origin

Natural Oils	% of Oil in Seed or Kernel	Melting point (°C)	(Caprylic octoic)	Caproic (Hexoic)	Caproic (Decoic)	Lauric (Dodecan- oic)	Myristic (Tetrad- ecanoic)	Palmitic (Hexade- canoic)	Margaric	Margaroleic	Stearic (n-octa- decanoic)	Oleic	Linoleic	Linolenic	Ricinoleic	Ara-chidic (Eicosa- noic)	Ara-chidic (Eicose-noic)	Behenic	Erucic	Tetracosanic	Any Other Special Fatty Acid
No of Carbon			8	10		12	14	16	17		18					20		22	22	24	
Coconut oil	63–65	21-27	5.0–9.0	0–0.8	6.0–10.0	44.0–52.0	13.0–19.0	8.0–11.0	-	-	1.0–3.0	5.0–8.0	0–1.-0			0–0.5	—	—	—	—	—
cottonseed seed oil	18–25	0-5	—	—	—	0.1	0.7	22			0.4-3.0	20	35-54	0.7	-	0.3		0.2	—	—	—
Cocoa butter	34-38	30-35	—	—	—	—	0.1	26	0.3		34	34	3	-	-	1	0.1	0.2	—	—	—
Canola oil	40–45	17-22	—	—	—	—	0.1	4.0	0.1	-	2	61	21	9	-	0.7	1	0.3	0.7	0.2	Palmitoleic (0.3)
Castor oil	40–45	12	—	—	—	—	—	2.0			1	7	3		87						Palmitoleic (0.2)
Corn oil	48	10	—	—	—	—	0.1	11.0	0.1	-	2	25	60	1	-	0.4	-	0.1	—	—	—
Chullu (wild apricot) seed oil	45-50		—	—	—	—	1.0-1.5	3.0-4.0	—	—	2.0-4.0	72.0–75	18.0–22	—	—	—	—	—	—	—	—
Ground-nut oil (penut oil)	45-55		—	—	—	—	—	6.0–9.0	—	—	3.0–6.0	52.0–60	13.0–27	—	—	—	—	1.0-3.0	—	—	Lignoceric 1-3
Hemp seed oil	30–35		—	—	—	—	—	5.0–7.0	—	—	1.0–3.0	11.0–13	54.0–60	24.0–26.0	-	-		-	-	-	-
Jojoba (hohoba) seed oil	45-50		—	—	—	—	—		—	—		0.55–0.77				28.0–31.0		-14.2			Palmitolic (0.25)

Karanja seed oil	27–39	—	—	—	—	—	—	3.7-7.9	—	—	2.4-8.9	44.5–71.3	10.8–18.3	—		2.2-4.7		4.2-5.	—	—	—
Linseed oil	40–44		—	—	—	—	—	5.0–7.0	5.0-7.0		1.0–3.0	11.0–13.0	54.0–60	24.0–26.0	—	—	—	—	—	—	—
Lard	43-48	36–42		0.1		0.1	2	26	0.4	0.2	14	44	10	0.4	0.2	0.7	0.1	-	-	-	Pentadecanoic(0.1) Palmitoleic (3)
Olive oil (virgin)	45–70	6	—	—	—	—	—	9	—	—	3	80	6	0.7		0.4	—	—	—	—	Palmitoleic (0.6)
Palm oil	30–60	26–30	—	—	—	0.1	0.5–2.0	32.0–45.0	0.1		2.0–7.0	38.0–52	5.0–11.0	—	-			0.1			
Palm kernel oil	44–65	26–30	3.0-5.0		3.0-7.0	40.0–52.0	14.0–18.0	7.0–9.0	0.1	0.1	1.0–3.0	11.0–19	0.5–2.0	—	—	0.1	0.1	—	—	—	—
Peanut oil	45–55	17–22	—	—	—	—	---	6.0–9.0			3.0–6.0	52.0–60	13.0–27	—	---	2.0–4.0		1.0-3.0			Lignoceric 1-3
Rapeseed oil	-10	17–22				0.1	1	4			1	19	1	19	----	0.7	7		41	1	Palmitoleic (0.3) Ecosadienoic (0.7)
Sunflower oil	-17	18					0.1	7	0.1		5	19	68	0.8		0.4	0.1	0.7			Palmitoleic (0.1)
Soybean oil	-16	22-31					0.1	11	0.1		4-	23	54	8		0.3		0.3			Palmitoleic (0.1)
Tallow	45-50	40-46				0.1	3	24	2	0.8	19	43	3	0.7	--	0.2	0.3	-	-		Myristoleic (0.9), Pentadecanoic (0.5) Palmitoleic (4)

Table: 2 Lipid materials existing in the marketplace with their HLB value, production methods and regulatory situation (Pandey and Kohli, 2018).

Excipient (Brand Name) and Manufacturer	HLB Value	Production Method	Regulatory Situation
Acconon® CC-6/ Abitec co	12.5	—	EP, NF, USP,
Acconon MC-8/ Abitec co	14		EP, NF, USP,
Brij® 97/ Croda	12.4		—
Captex® 355/ Abitec Co	1	Glycerol (plant sugars) esterification with combinations of caprylic (C8) and capric (C10) FAs from palm or coconut kernel oils	USP
Captex® 200/ Abitec Co	–5	—	—
Capryol™ PGMC90/ Gattefosse	5	—	USP 31-NF 26 Supp 1
Capryol™ 90/ Gattefosse	6	—	USFA, FCC, USP-NF, JSFA
Cremophore® EL/ BASF	12–14	—	USP
Cremophore® RH40/ BASF	14–16	The reaction of tri-hydroxys-tearate with 40-45 moles of ethylene oxide (EO)	FDA inactive ingredients
Cremophor® A25/ BASF	15–17	—	-
Capmul® MCMC8/ Abitec Co	5–6	Glycerin esterification with C_8-C_{10} FA obtained from palm kernel oil or coconuts	EP
Capmul® MCM C10/ Abitec Co	5–6	Glycerin esterification with C_8-C_{10} FA Obtained from palm kernel oil or coconuts	EP
Capmul® MCM/ Abitec Co	5–6	Glycerin esterification with C_8-C_{10} fatty acids from coconut or palm kernel oil	EP
Gelucire® 50/13/ Gattefosse	13	—	IIG, USP-NF, EP, USFA
Gelucire® 44/14/ Gattefosse	14	Alcoholysis of saturated oils largely composed of lauric acid triglycerides with polyethylene glycols	USP 29-NF 24 IIG/EP
Imwitor® 742/	—	—	USP/NF

KemCare			
Imwitor® 928/ KemCare	—	—	USP/NF
Labrasol®/ Gattefosse	14	Glycerol and polyethylene glycol esterification with caprylic acid and capric acid, or glycerol esters and EO condensate esterification with caprylic acid and capric acid	USP-NF, EP
Labrafil® WL 2609BS/ Gattefosse	6	The usage of macrogol with an average relative molecular weight of 300 to 400 in the partial alcoholysis of an unsaturated oil primarily composed of linoleic acid triglycerides. .	—
Labrafil® M2130CS / Gattefosse	4	—	EP
Labrafil® M2125CS / Gattefosse	4	Partial alcoholysis of unsaturated oils with polyethylene glycol, primarily including triglycerides of linoleic acid, via Glycerol and polyethylene glycol esterification with fatty acids	USP-NF, EP
Labrafil® M1944CS/ Gattefosse	4	Partial alcoholysis of unsaturated oils with polyethylene glycol, primarily including oleic acid triglycerides, via, Glycerol and polyethylene glycol esterification with fatty acids	USP-NF, EP
Labrafac® CM 10/ Gattefosse	10	—	—
Labrafac® PG/ Gattefosse	2	—	USFA, E477, USP-NF Pending
Labrafac® Lipo-phile WL 1349/ Gattefosse	2	C_8 and C_{10} vegetable oil fractionation (mostly coconut and palm kernel)	JPED, USP-NF, JSFA
Lauroglycol™ 90/ Gattefosse	5	—	EP
Lauroglycol™ FCC/ Gattefosse	4	The mono and di-esters of lauric acid in propylene glycol are mixed.	EP
Maisine™ 35-1/	4	Glycerolysis of vegetable	USP-NF,

Gattefosse		oils (partial) (linoleic acid triacylglycerols mostly)	GRAS, EP, E471, FCC, JSFA
Myrj® 45/ Gattefosse	FCC	The polymerization of EO is catalyzed by alkali, which is then neutralized.	USFA
Miglyol® 840/ Sasol	—	—	EP, USP-NF, JCIC,
Miglyol® 810/ Sasol	—	—	USP, BP,, NF
Miglyol® 818/ Sasol	—	—	—
Miglyol® 812/ Sasol	15.36	—	BP, USP, NF
Plurol oleique® CC497/ Gattefosse	6	Polyglycerin (mostly triglycerin/hexaglycerin) with oleic acid esterification	FCC, E471, JSFA, USFA
Precirol™/ Gattefosse	3.3	Glycerin Esterification with food-grade oleic acid in the presence of an appropriate catalyst	EP, USP-NF, GRAS, JSFA, FCC, E471
Plurol® Diisostearate/ Gattefosse	4.5	Polyglycerol (mostly triglycerol) with isostearic acid esterification	EP
Transcutol® HP/ Gattefosse	4.8	Distillation after EO and alcohol condensation	EP, USFA, USP-NF
Transcutol® P/ Gattefosse	4.2	Distillation after EO and alcohol condensation	HG, EP, USP-NF, USFA

USP*- United States Pharmacopeia, NF-National Formulary, EP* -European Pharmacopoeia, USFA*-Unsaturated Fatty Acids, USA-NF*-United States Pharmacopeia in combination with National Formulary, USAFA*-United States Pharmacopeia National Formulary, FCC-Food Chemicals Codex, JSFA*-Journal of the Science of Food and Agriculture, JPED*-Japanese Pharmaceutical Excipients Directory, IIG*-Inactive Ingredient Guide, JCIC*-Japanese Cosmetic Ingredients Codex

4. Lipid fate in the human body (*In-vivo* Mechanism)

A typical adult diet contains roughly 60-80 g of fat per day. Furthermore, the cholesterol, phospholipids & lipids that line the membrane of differentiated intestinal cells and bacteria make up the 40–60 g of endogenous fat (Hinsberger and Sandhu, 2004). According to this, a typical digestive system of an adult may hydrolyze in between 100 to 140 grammes of fat every day. The bioavailability of pharmaceuticals and how they dissolve in the gastrointestinal tract are mostly determined by the intraluminal processing that lipids undergo before absorption. In the existence of a healthy gastrointestinal system, having a solid understanding of the path that lipids take from the gastrointestinal lumen to the circulation system is essential for correctly interpreting the bio-pharmaceutical belongings of oral formulations that are found on lipids and for ensuring that effective product development occurs (Ljusberg et al., 2005).

Lipid digestion in the GIT is a critical process that plays a significant role in the bioavailability of lipophilic drugs delivered via lipid-based formulations. The GIT consists of several regions, including the stomach and the small and large intestines, each with distinct pH levels and enzymatic activities that affect the digestion and absorption of lipids. The stomach primarily digests proteins, some lipid digestion begins here due to the action of gastric lipase. Gastric lipase is an enzyme that breaks down short- and medium-chain triglycerides into diglycerides and free fatty acids. While majority of lipid digestion occurs in the small intestine. The pancreas secretes pancreatic lipase, colipase, and bile salts. These enzymes and bile salts emulsify and digest lipids. Bile salts aid in the emulsification of larger lipid droplets into smaller micelles, increasing the surface area for enzymatic digestion. Pancreatic lipase then acts on these micelles, breaking down triglycerides into monoglycerides and free fatty acids, which are more readily absorbed as represented in **Figure 3 (Pouton and Porter 2008, Porter et al., 2008)**. As a result, this section aims to make understanding the whole procedure easier by segmenting the process in three distinct parts:

(1) digestion, (2) absorption, and (3) circulatory uptake

Digestive Phase: The physical disintegration of the lipid formulation into an emulsion that is coarse (with 0.5 lm lipid droplets) and has a wide outer surface due to the shearing generated by antral contractions, retropulsion, and stomach emptying is the first step in the digestive phase. In next step gastric lipase breakdowns fatty acid glyceryl esters. This enzyme is released by the major cells present inside the stomach and is able to function in an environment that is acidic. The transformation of TGs into their more polar counterparts, monoglycerides (MGs), and fatty acids is a process that is referred to as enzymatic hydrolysis (FAs). Lipase cleaves both of the ester linkages that are present on the TG molecule, which results in the formation of a diglyceride molecule as well as one free FA. Following this step, one MG molecule and two free FAs molecules are produced (**Figure 3**). The lipids that have not been digested, along with the scattered products of lipid breakdown, are drained into the duodenum (Carey et al., 1983). The low pH of the stomach causes the mucosa of the

duodenum to secrete fluid into the portal circulatory system. This system empties the digestive organs, including the spleen & the pancreas, also it supplies blood fluid to liver through the portal vein of hepatic system. Because of this, the pancreas is stimulated to manufacture bicarbonate and then releases it into the duodenum, along with lipase and co-lipase, in an effort to generate an environment with a pH that is neutral. This, in turn, stimulates more activity from the pancreatic lipase and co-lipase enzymes. Cholecystokinin is triggered to be discharged in the portal circulation when FAs are present. This triggers the production of TG lipase and co-lipase by the pancreas. Both of these enzymes are essential for the digestion of TGs that are found within emulsified particles. FAs and MGs are beneficial emulsifiers due to the fact that they are partially ionised and aid to facilitate the interaction of the lipase-co-lipase composite with the exterior of the emulsion (Borgström, 1980; Bernbäck et al., 1989). When lipolytic molecules are produced, this means this autocatalytic process is called lipolysis that has the potential to improve emulsification. Both enzymes are water-soluble, and they perform their hydrolysis of TGs to MGs and FAs at the water/oil interface of the particle (Kozlov and Helfrich 1992; Embleton and Pouton 1997). The synthesis of mixed micelles marks the completion of the digestive phase, which was initiated via association of TGs and FAs with bile salts; however, some of them may still be capable of forming vesicles after digestion during the pre-absorption stage (Ollivon et al., 1988, Paternostre et al., 1988). To improve the efficacy of the formulation, emulsifications resolubilize the release of drug from the preparation by dissolution or precipitation into the GI medium into micelles or mixed micelles (Fatouros et al., 2007, Kossena et al., 2007). Generally, *In-vivo* solubilization ability of a medicine is affected by its lipophilicity, chemical structure, and the types of endogenous and external lipids involved in the colloidal species creation (Kossena et al., 2003). Even doses as low as 2 grammes of long-chain lipids are sufficient to stimulate the gall bladder contraction and increase accumulation of biliary lipids in the colon, all without significantly slowing the rate at which the stomach is emptied. The same amount of medium-chain lipid on the other side, has been shown to enhance the concentration of biliary-derived lipids in the gut with minimal effect on gallbladder contraction (Kossena et al., 2007). A lipid emulsion that contains 10 grammes of glyceryl monooleate can induce a spike in danazol medication absorption that is comparable to the rise that is seen in healthy patients after the medication is administered along with a heavy meal (Charman et al., 1993). In order to increase the rate of lipolysis, dispersible formulations such SMEDDS/SNEDDS are used. Enzymes function better with dispersible system. Sandimmune and Sandimmune Neoral are two examples of this, and (Ptachcinski et al., 1986; Kovarik et al., 1994), these formulations ensure continuous bioavailability while also maximising the rate at which the medication partitions into the aqueous fluids of the digestive tract. In pharmaceutical science, there are formulations designed to optimize the breakdown of lipids during the digestive phase, thereby enhancing drug absorption. SEDDS and SMEDDS are prime examples of such formulations. These systems are carefully engineered to form fine lipid-based emulsions upon contact with gastrointestinal fluids, closely mimicking the natural digestion of dietary lipids. As these emulsions form, they efficiently break down lipids into fatty acids and monoglycerides, which can, in turn, solubilize poorly water-soluble drugs, enhancing their absorption. By capitalizing on this natural digestive process, SEDDS and SMEDDS optimize drug solubility and, consequently, bioavailability. They have proven effective for numerous drugs and are an innovative approach for improving the oral delivery of lipophilic compounds (Hauss 2007).

Absorptive Phase: Mixed micelles, vesicles, micelles & free FAs are the types of colloidal entities that are transported through the membrane of an enterocyte using either passive diffusion, assisted diffusion, or active transport. These colloidal entities are formed as a end

product of lipid digestion and come in a variety of different forms. The fatty acids are transported to the smooth endoplasmic reticulum (ER) from the apical membrane located in cytoplasm by a protein that binds to fatty acids. As a consequence of this, a concentration gradient causes an increase in the amount of FA that is absorbed in cell through a process which is mediated by a suitable carrier (Stremmel, 1988). After being resynthesized in smooth ER as TGs & phospholipids, respectively, FAs and MGs are then transported to the golgi apparatus & stored in secretory vesicles before being exocytosed through the basolateral membrane and discharged into the extracellular environment. Another important step in the process is when the free drug that was absorbed interacts with the intestinal lipoproteins (chylomicrons) that are found inside the enterocyte. Due to the fact that chylomicrons are colloidal and relatively large (1 lm in diameter), the lipophilic substance is transported through the lymphatic system of the intestinal tract in a more favourable manner (Harrison 2005; Charman and Porter 1996; Ichihashi et al 1992). Cytochrome P450 3A4 (CYP 3A4) is a key phase I drug metabolising enzyme that can be found in high concentrations in cells known as enterocytes that are situated in humans near the villus tip of the small intestine. Lipids can interact with CYP3A4, a key enzyme in drug metabolism, through several potential mechanisms. Firstly, some lipids, particularly long-chain fatty acids, may act as modulators of CYP3A4 activity. They can induce conformational changes in the enzyme, either inhibiting or activating its function, depending on the specific fatty acid composition and structure. Secondly, lipids, when incorporated into LBFs, can influence drug solubility and dissolution rates. This alteration in a drug's physical state can, in turn, affect its interactions with CYP3A4. Thus, LBFs may alter drug bioavailability by delaying drug release in the gastrointestinal tract, impacting the time window during which drugs are exposed to CYP3A4 in the liver and intestine. These interactions with CYP3A4 can ultimately influence drug absorption and metabolism, potentially leading to variations in drug efficacy and safety. Investigations carried out in a number of different research facilities have demonstrated that the aforementioned enzymes play an important part in elevating the medication's bioavailability as they are co-administered along with fat. These findings point to an additional mechanism by which lipids improve the drug's absorption as well as its bioavailability Trevaskis et al., 2006, 2006; Wacher et al., 1995, 2001). On the other hand, the specific mechanism that underlies this phenomenon is still a mystery. Only a few specialists believe that lipids can prevent the growth and function of these enzymes. Other researcher's opinion that lipids can shield medication fragments from the enzymes (Furuhashi et al., 2014; Wasan et al., 2009).

Circulatory uptake: Mostly drugs that are taken orally enter the systemic circulation through a process called portal blood absorption. However, the metabolism can be circumvented by a number of tremendously hydrophobic drugs (log P > 5, solubility in TG > 50 mg/ml), which allow these treatments to enter the systemic flow via the lymphatic pathway. As a consequence of this, drugs that are rapidly metabolised and are lipophilic can be attractive drug delivery applicant based on lipids. Compounds with greater bioavailability in the existence of lipids (dietary or LBF) get absorbed through the lymphatic system with the LCT lipid core of colonic lipoproteins produced in the enterocyte after re-esterification of free FAs and MGs. This allows the compounds to be absorbed in a manner that is similar to how they would be absorbed in the presence of lipids. The peripheral circulation is responsible for the majority of the absorption of short-chain TGs. Co-administration of lipids with a medication is necessary for lymphatic transport because it stimulates the production of lipoproteins (Thomson et al., 1989). It is not possible for TGs and phospholipids to enter the circulatory system directly, despite the fact that portal blood has a concentration that is five hundred times higher than that of intestinal fluid. Because of the enormous size of their

molecules, they are unable to move through the capillary fenestration gaps. Squamous epithelial cells form a single layer of lymphatic capillaries walls. Because of the capillary's thin wall, tissue fluid (also known as interstitial fluid) can enter the lymphatic capillary from the interstitial space. In addition, the endothelial architecture of lymphatic arteries makes it easier for the size-selective transfer of big molecules such as chylomicrons, which are restricted in their movement across the endothelium of blood capillaries (Leak et al., 1976). According to the findings of several studies, the length of the free FA chain, in addition to the content & size of precursor pool lymph lipid within the enterocyte, all have a significant role in the process of medication administration via the lymphatic system. Free FAs with shorter chain lengths than 612 carbons are mostly immersed by the portal circulation, while Free FAs with longer chain lengths are carried and re-esterified *via* the lymphatic system (Trevaskis et al., 2006). In addition, raising the level of unsaturation causes lymph lipoproteins to be of a larger size, which favourably increases lymphatic absorption (Cheema et al., 1987, Bergstedt et al., 1990). After that, the lymph fluid is expelled through the thoracic duct and into the subclavian vein at a rate of approximately 3 litres per day on average (Zuther et al., 2017), protecting the medicine from being metabolised by the liver. The lymphatic system, which functions as the major mode of metastatic dispersion for a variety of solid cancers and viruses as well as the fundamental systemic transport channel for B and T cells, can be a (Pouton 2006; Porter and Charman 2001), possible drug delivery target for medications used in immunomodulation, cancer treatment, and other related treatments (Garzon et al., 1983; Pantaleo et al., 1993, 1994; Umeda et al., 2005; Cense et al., 2006; Spiegel et al., 2006; Arya et al., 2006; Von Messling et al., 2006; Lalanne et al., 2007;; kessel and Toubi, 2007). Because the concentration of surfactant may be reduced lower its CMC value and the micelle may disassociate into monomers after being diluted with bulky capacity of lymph or blood, the medication, which is being delivered through the systemic circulation in the form of vesicles, micelles or mixed micelles, may be accessible in its free form. This is for the reason that the micelles are being delivered in micelles or mixed micelles form. It is possible for the medication to stay intact for longer periods of time when it is given in lipid vesicles, which results in sustained drug release. **Figure 3** is a diagrammatic illustration of the many different ways that lipids affect the bioavailability of medications. As was just mentioned, the process by which lipids are taken in by the enterocytes of the small intestine from the lumen of the gut and then diffused into the circulation is a difficult one. On the brush border of the apical membrane of the enterocyte, the absorption of lipids is controlled by membrane channels. Additionally, a variety of proteins thought to be involved in FA absorption have been found. Intracellular trafficking proteins help promote the transference of lipids from the membrane of plasma to the endoplasmic reticulum (ER). After being absorbed into the ER, lipids undergo resynthesis and are then packed into chylomicrons; this process is dependent on the activity of apoB and the microsomal triglycerides transport system.

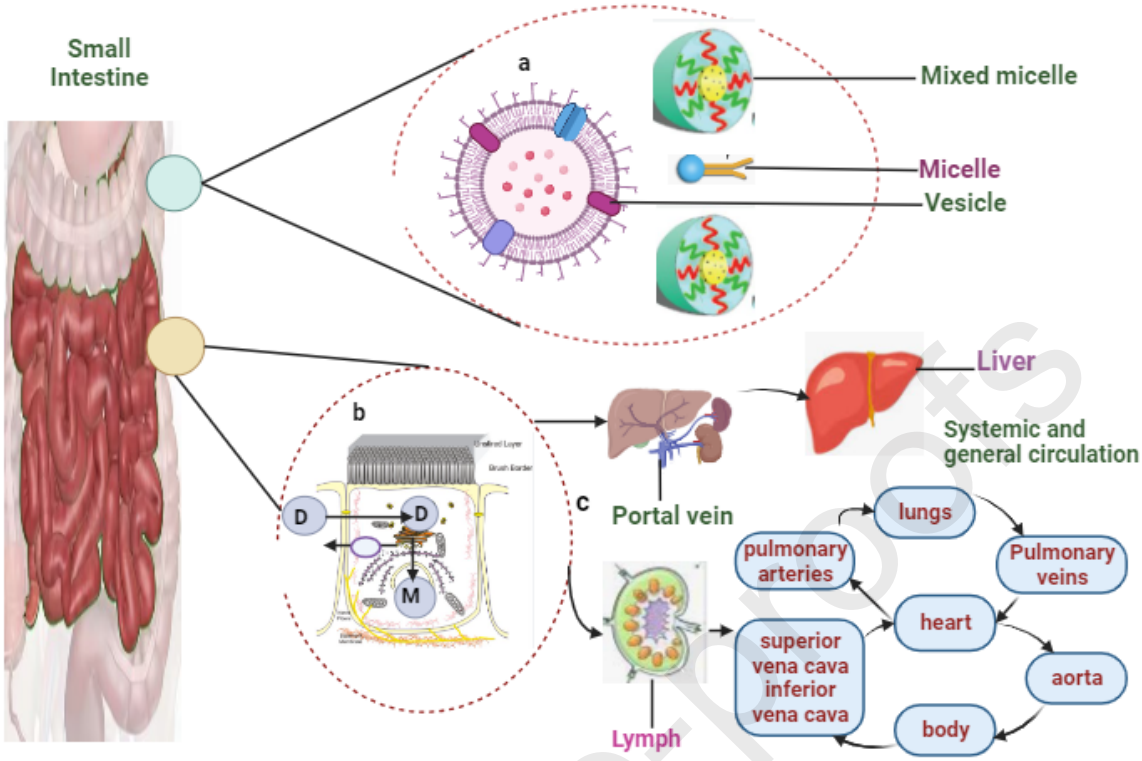


Figure:3 The following mechanisms for improved absorption in the presence of lipids have been proposed: The following mechanisms of increased systemic availability in the manifestation of lipids have been proposed: (a) dissolution of drug in the gastric fluid via the creation of colloidal species including vesicles, mixed micelles, and micelles; (b) intervention of enterocyte-based transportation and metabolic activities, which could affect drug intake efflux, drug behaviour, and the creation of metabolites (M) first-past by the enterocytes; and (c) limited lymphatic uptake, decreasing metabolism

5. Morphology of lipid digestion products

A range of colloidal species, comprising vesicles, micelles, and mixed micelles, are produced during lipid digestion in the colon. Vesicles are lamellar phases that self-assemble from phospholipids (like phosphatidylcholine) that are insoluble in water. Until they reach a critical micellar concentration, surfactant molecules disperse in water as monomers. At that moment, the moieties assemble themselves to produce micelles. Mixed micelles (**Figure 3**) are micelles consisting of multiple surfactant systems (Weng et al., 2014). In the presence of lipase action, interactions among oil globules and BS media leads to the development of vesicles via intermediate by products. In the duration of digestion, bilamellar vesicles develop and they frequently turn to unilamellar vesicles. As the surfactant to lipid ratio rises, they freely break into micellar as well as mixed micellar phases (Weng et al., 2014; Qureshi et al., 2015). Although lipolysis yields dispersed as uni-lamellar and multi-lamellar vesicles are accountable for fat absorption through the later part of the SI, the phase transition develops the thermodynamic conditions that are best suited for effective lipid absorption from the SI into the BS insufficiency (Hernell et al., 1990). Investigations on quasielastic dispersion of light have demonstrated that unilamellar vesicles possess radii between 200 and 600, while micelles have ex vivo average hydrodynamic radii around 640. Micelles remained also found to be more broadly effective at lipid solubilization than unilamellar vesicles (Hernell et al., 1990). Cryogenic electron beam microscopy of a SNEDDS through *In-vitro* digestion

showed a complete chain of changes in mode in the process of digestion, including micelles measuring around 10 nm being seen throughout all phases (Fatouros et al., 2007).The results confirmed the hypothesis that micelles multilamellar as well as unilamellar vesicles might be exist jointly (Qureshi et al., 2015). Subsequently an oil emulsion hydrolysis, light microscopy showed "a viscous isotropic phase" (Carey 1983) that was followed by "a liquid lamellar crystalline phase containing calcium and ionised FAs known as calcium soaps." In a study on *In-vitro* lipolysis, for the purpose to explain multiple phases, X-ray beam scattering analyses have additionally been effectively utilised as a selection method (Greenberger et al., 1966). The medications partitioning to lipophilic products and subsequently, the *In-vivo* activity of formulations, can be explained with the help of further research into the morphological characteristics of the basic variations that take place throughout the process of lipid digestion.

6. Procedures for making oral formulations based on lipids.

The field of LBFs has witnessed significant advancements in recent years, with several technologies holding the potential to substantially improve drug absorption and bioavailability. One such innovation is the development of lipid nanoparticles, including solid lipid nanoparticles (SLNs) and nanostructured lipid carriers (NLCs). These nanoparticles offer improved drug encapsulation, controlled release, and enhanced stability, ultimately leading to enhanced drug absorption. Additionally, lipid-based nanocarriers such as liposomes, which have been under constant refinement, have shown promise in delivering a wide range of drugs, from anticancer agents to vaccines, by enhancing drug solubility and providing targeted drug delivery. Selecting and optimizing LBFs in pharmaceutical formulations is a nuanced process that demands careful consideration of several factors. Formulators should begin by comprehensively assessing the physicochemical properties of the drug, paying particular attention to solubility, stability, and release kinetics. The choice of lipid source, whether natural, synthetic, or semi-synthetic, should align with the drug's characteristics and intended application. The composition, including the type of lipids and surfactants, should be meticulously balanced to ensure compatibility with the drug and desired release profiles. As well, the physical state of the lipids, such as solid lipids, nanoemulsions, or liposomes, plays a vital role in controlling drug release rates. Thus researcher have a holistic approach, combining drug properties, lipid selection, and formulation design, is essential for developing effective LBFs.

a) SEDDS/SNEDDS/SMEDDS

These delivery systems are iso-tropic blends of synthetic or natural oils, solid/liquid emulsifiers, or one/mixture of hydrophilic co-solvents/co-emulsifiers (Pouton et al., 2000, Shah et al., 1994). They disseminate freely within the GIT, and the gastrointestinal peristalsis movement be responsible for the agitation required for process of self-emulsification (Pouton et al., 2000). To create SEDDS/SMEDDS, it is necessary to analyse a variety of excipient combinations for the most effective, stable, and permeable combination. To help in the categorization of formulations with comparable components, Pouton et al. invented the lipid formulation classification system (LFCS) to address these problems as shown in **Table 3**. Based on their formulation composition and the possessions of dilution and absorption on their capacity to avoid drug saturations, LBF are divided into four categories by the classification system. Medications that have been solubilized in triglycerides, Type I systems comprise mixed glycerides with an O/W emulsion maintained *via* sufficient number of emulsifiers, like 1.2% (w/v) lecithin as well as 1% (w/v) polysorbate 60 (Cuine et al., 2008).

These systems frequently possess poor initial aqueous dispersion and require pancreatic lipase/colipase assimilation, higher amphiphilic lipid digestion metabolites will be synthesised and medication transport within the colloidal fluid phase will be enhanced by the GIT. However, this technique is frequently effective for formulations that are readily assimilated, and lipid digestion might promote basic formulation dispersion and drug solubilization. Consequently, when the solubility of a drug in Lipids/oil is enough to permit the assimilation of the suitable therapeutic dose size, Type I lipid formulations are an easy alternative for highly lipophilic drugs. When contacted with water, Type II lipophilic compositions self-emulsification to produce fine O/W emulsions. These formulations are also known as SEDDS. Surfactant concentrations of greater than 25% (w/w) frequently cause self-emulsification. However, the formation of crystalline gelatinous liquid at the oil-water interface can hinder the development of emulsification at greater surfactant levels (> 50%–60% (w/w) reliant on ingredients) (Chatterjee et al., 2016, Rodríguez et al., 2015). In order to provide single-unit dosage forms, poorly water-soluble medications can be incorporated in soft or hard gelatine shells capsules. This is made possible by the SEDDS (Gershanik et al., 2000). By creating large interfacial areas that enable effective drug partitioning among the oil globules and the water phase where absorption takesplace, Type II LBF avoid the delayed dissolving step typical in solid dosage form (Lee et al., 2015). Considering maximum plasma concentration (Cmax) and area under the curve (AUC) values that are at least three times higher than those of standard dose forms, SEDDS formulations exceed them in vivo. In the GI lumen, enhanced drug solubilization and immediate drug release have been correlated to enhanced drug solubility. The major components of Type III formulations, often referred to as SMEDDS, comprise hydrophilic emulsifiers (HLB > 12), cosolvents and oils. Formulations of Type III are additional distributed into Type IIIA and IIIB formulations. Type IIIB contains less lipids and more hydrophilic surfactants and cosolvents than type IIIA. The potential risk of medication precipitated during dispersion is increased in Type IIIB preparations because of too much hydrophilic surfactants as well as cosolvents concentration. Marketed type III preparation contains cyclosporin Neoral® (Novartis) as best-suited example. This mixture comprises of corn oil glycerides, surfactant cremophor RH40, co-solvent glycerol, propylene glycol, and ethanol. **Table 3** lists the many kinds of oral lipid formulations, the ingredients used, and the advantages and disadvantages of each (Jannin et al., 2008; Chavan et al., 2015).

Table: 3 Classification of lipid-based formulation their characteristics, advantages and Disadvantages (Pouton et al., 2000, Tokumura et al., 1987).

Formulation Class	Class 1 (Lipid solution)	Class II	Class IIIA (Fine emulsion)	Class IIIB (Microemusion)	Class IV
Marterials used in formulation	Oils without surfactants	Oils and O/W soluble surfactants	Lipid/Oils, surfactants-co-surfactant ratio, co-solvents (both Aqueous soluble and insoluble component)	Lipid/Oils, surfactants-co-surfactant ratio, co-solvents (both Aqueous soluble and insoluble component)	Water-soluble surfactants and co-solvents(no oils)

Characteristics	Not-dispersiable,	Emulsification (SEDDS) with Aqueous insoluble substances	SEDDS/SNEDDS/SMEDDS molded using aqueous solvable substances	SEDDS/SMEDDS formed using aqueous soluble substances and amount of oil is less	Disperses classically to produce a micelles solution
Digestion characteristic	Requires digestion	Ingested easily	Ingestion not essential	Ingestion not compulsory	Partial Ingestion
Advantages	Simple, GRAS, Capsule-compatibility.	Unlikely, On Dispersion loose solvent capacity	On dispersion, clear or almost clear dispersion	On dispersion, clear or almost clear dispersion	Formulation have good solvent capability
Disadvantages	Poor solvent capability	Relatively Coarse O/W dispersion, ingestion probable but not decisive	On dispersion, possibility is loose of solvent capability or ingestion	On dispersion, possibility is loose of solvent capability or ingestion	On dispersion, possibility is loose of solvent capability
Example	Etomidate (anesthetic) (Geng et al., 2021)	-	Cyclosporin (an immunosuppressant), (Keohane et al., 2016)	Saquinavir (an antiretroviral). (Hosny et al 2023)	Amphotericin B (antifungal) (Faustino and Pinheiro, 2020),

b) Solid Self-Emulsifying and solid Micro Drug Delivery System

SEDDS solution can be converted to dry powders are filled into hard capsule shells, granules, pellets and tablet, however they must be added directly into capsules. A carrier may contain a higher proportion of liquid SEDDS/SMEDDS (up to 70%). This preparation facilitates flowability and manufacturing of tablets by high content consistency for both capsules as well as tablets. The formulator's possibilities are greatly increased by using this method. High-pressure homogenization, supercritical fluid-based techniques, spray chilling, adsorption on solid support, melt extrusion, spray drying as well as melt granulation are all relatively simple methods. Extrusion-spheronization was recently used for making self-emulsifying mix-containing pellets (Čerpnjak et al., 2015; Desai and Nagarsenker et al., 2013; Kohli et al., 2010). This technique increases drug absorption by providing the *In-vivo*

advantages of a SEDDS as a tablet. The further benefit of this technology is that it permits liquid SEDDS of high drug loading on a carrier, thereby improving the content (granules) uniformity. The presence of a drug within the lipid preparation, whether in a dissolved or dispersed state, and the adherence of the liquid SEDDS to a solid carrier should not affect the solubilizing capabilities of the final solid dosage form in terms of its effectiveness and efficiency. At the industrial level, the formulation procedure is incredibly forthright and encounters some challenges including one of the primary hurdles is maintaining the drug's solubility and stability as it shifts from a liquid to a solid state. This transition often necessitates the addition of solid carriers or excipients, which must be carefully chosen to ensure compatibility with the drug and the lipid-based system. Another challenge is achieving uniform distribution of the drug and lipid components within the solid dosage form, which is essential for consistent drug release and absorption. Furthermore, the control of release kinetics in solid forms may require sophisticated formulation design and, in some cases, specialized manufacturing techniques. Nevertheless, the advantages of solid formulations, including improved stability, ease of handling, and enhanced patient compliance, make these challenges worth addressing. Successful transitions from SEDDS/SMEDDS solutions to solid forms can significantly contribute to the development of effective and patient-friendly LBFs. This method consequently enhances the manufacturing, design, and performance of products (Aungst 2010).

c) Lipid as colloidal medication carriers:

The effectiveness of both well-known and novel medicaments has been enhanced by the use of lipophilic colloidal medicament carriers called nanoparticlesas well as liposomes. Liposomes are vesicles that contain an aqueous phase and one or more phospholipid bilayers. They are categorised as small unilamellar vesicles (SUV), large multilamellar vesicles (MLV) and unilamellar vesicles (LUV) based on their mass and the total lipid bilayers. Liposomes, spherical lipid vesicles with a phospholipid bilayer structure, offer several distinct advantages in pharmaceutical and drug delivery applications. One of their primary benefits is their exceptional versatility. Liposomes can encapsulate a wide range of drugs, including hydrophilic and lipophilic compounds, making them suitable for various therapeutic agents. They enhance drug stability and solubility, protecting drugs from enzymatic degradation and harsh gastrointestinal conditions. Additionally, liposomes enable targeted drug delivery, allowing for the site-specific release of drugs, which reduces off-target effects and minimizes side effects. Moreover, they are biocompatible and biodegradable, minimizing the potential for adverse reactions. These attributes, combined with their ability to improve drug bioavailability, have established liposomes as a valuable tool in the pharmaceutical industry for enhancing drug performance and therapeutic outcomes (Chen et al., 2009). For enhancing drug stability, solubility as well as absorption of medication that are only partially water-soluble, liposomes may be used for oral drug/protein administration (Czogalla 2009, Ariën et al., 1993). Some studies have exposed that enzymatic action in the duodenum and Bile salt damages the lipid bilayers of the majority of liposomes, allowing the release of drug (Jesorka et al., 2008). Certain researchers contend that liposomes have the potential to shield drugs that are sensitive to the harsh GI environment (Ariën et al., 1994; Woodley, 1985). These liposomes are composed of phospholipids with a multilamellar phase structure. The most durable multilamellar liposomes are those containing both cholesterol and phospholipids, with phase transition temperatures exceeding 37°C. Although several techniques have been used to make liposomes, the most popular ones are high-pressure extrusion, solvent injection, detergent elimination, reverse-phase evaporation and film hydration (Schwarz et al 1994; Muller et al., 2000). However, If the drug is not stable in

the hydrophilic phase, liposomes produced via any of the techniques listed above can be freeze dried by using the suitable cryoprotectants in order to proliferation of the shelf life of product.

SLN based oral medicine administration has drawn a lot of interest during the past 20 years (Muller et al 1997, 2008). In comparison to traditional polymeric nanoparticles, On the other hand, SLNs offer several notable advantages in the realm of LBFs. One of their primary advantages is enhanced drug stability. The solid lipid matrix provides a protective environment, shielding drugs from degradation due to environmental factors such as light, heat, and moisture. SLNs also excel in terms of controlled release, allowing for the sustained release of drugs over time. This is particularly beneficial for drugs that require long-lasting therapeutic effects or sustained drug levels in the bloodstream. Also, SLNs have the capacity to encapsulate both lipophilic and hydrophilic drugs, making them a versatile choice for a wide range of pharmaceutical compounds. They are biocompatible, reducing the risk of adverse reactions, and can be easily incorporated into various dosage forms, including oral, topical, and parenteral formulations. SLN are a safer and more advantageous approach because they are produced from physiologically suitable lipids. P-gp inhibition and ATP diminution can overcome multidrug resistance. P-gp, a crucial efflux transporter, plays a pivotal role in drug absorption and distribution within the body. Inhibiting P-gp is a valuable strategy to improve drug bioavailability, especially for drugs prone to P-gp-mediated efflux. P-gp inhibition can occur through various mechanisms. Competitive inhibition involves a drug binding to the P-gp binding site, competing with the substrate drug for efflux. Non-competitive inhibition, on the other hand, can modify the P-gp protein's conformation, preventing it from actively pumping out the substrate drug. Mechanisms can also include altering the expression of P-gp by influencing gene regulation or using excipients that modulate P-gp activity.

According to *In-vitro* studies using paclitaxel and doxorubicin-loaded lipid nanoparticles on P-gp-overexpressing human carcinoma cells (Dong et al., 2009, Ugazia et al., 2002) indicating their potential to enhance the therapeutic effects of medications. Oral administration of lipid nanoparticles containing medications like tobramycin, cyclosporine A, pyrazinamide, rifampicin, idorubicin, isoniazid and camptothecin as well as proteins like nanoparticles having lectin-modified insulin-containing calcitocin and SLN results in the enhancement of bioavailability of In- vivo studies. There are several prominent methods to produce SLN, including microemulsion, high-shear homogenization, ultrasonic, solvent emulsification, and the high-pressure homogenization (both cold and hot homogenization) technique. A common dosage form, like powder, tablets, capsules as well as pellets can be combined with SLN to produce an aqueous dispersion, which can then be administered. The hydrophilic SLN dispersion might be also spray-dried to form powder or combination with the essential additives before compaction into tablets, or it can be used as the granulation solvent in granulation process. In the extrusion process, SLN dispersion also be utilized as a wetting agent to produce pellets (O'driscoll and Griffin et al., 2008). SLN granules can also be mixed with liquid PEG and placed inside of soft gelatin capsules, or put into firm gelatin capsules. Powders that have been lyophilized or spray-dried can also be placed within sachets. The physical properties of the resulting SLN powder, such as bulk density, flow property, strength, compressibility and waxy nature that can resist compression force and temperatures, must be determined prior to making the final dosage.

7. Excipient screening for lipid formulations:

A main challenge in designing of any oral dosage form is sustaining drugs solubility inside the GIT, and increasing solubility of the medicament at the main absorptive site in the gut (Agrawal et al., 2012). For the effective formation of SEDDS/SMEDDS, a number of characteristics are necessary, including a high log P value, having low melting point as well as dose (Pandey et al., 2018; Kohli et al., 2010; Lipinski et al., 2012). A medicine must have log P value > 5 in order to be considered effective, according to Lipinski's qualitative predictive model (Lipinski et al., 2012). Effective self-emulsification be subject to on a few key factors, including:

1) The drug solubility in excipients approved by pharmaceutical industry (cosurfactants, lipids and surfactants); 2) The oil-surfactant pair's characteristics; 3) The ratio of oil to surfactants and co-surfactant concentration and 4) Temperature of self-emulsification. It is necessary to analyse drug excipients for compatibility, solubility and stability before selecting the best lipid system(s). A number of preliminary discoveries have shown a lack of incredibly specific pharmaceutical excipient combinations that result in effective self-emulsifying systems (Shah Kang et al., 2004; Kommuru et al., 2001). However, the system's total solubilizing ability should take preference over the medicine's solubility in its individual components. Component selection is influenced by multiple significant variables: A). Maximum medication loading should be achieved. Lipid droplets are believed to speed up digestion and lead to quicker and even drug release and permeation since globules surface area is in reverse related to droplet size. An optimal condition till the drug can be absorbed from the GIT is necessary for the self-emulsifying formulations' enhanced drug absorption (Shah Kang et al., 2004; Kommuru et al., 2001). B). Achieving an ideal globule diameter and self- emulsification time duration in the stomach acidic environment for optimal absorption. Droplet size distribution may change as a result of the drug substances interference with the process of self-emulsification, and this change will depend on the drug concentration. Particularly, emulsions with small oil globules are further susceptible to changes brought on by the addition of the medicinal component in more complicated formulations. Therefore, preformulation solubility and phase-diagram study are essential to formulate an ideal SEDDS (Shah Kang et al., 2004; Kommuru et al., 2001; Jaiswal et al., 2015). C). Variations in emulsion droplet size in correlation with aqueous medium electrolyte concentration and pH. D). Avoiding drug metabolism or degradation in a physiological state. Hydrophobic drug compounds that have been dispersed in pure cosolvents such as polyethylene glycol and propylene glycol. The mixture's solvent capacity decreases almost logarithmically when the formulation is diluted when it is combined with water. The medication therefore precipitates. Upon dispersion in Type IIIA LBF, for instance, a drug solubilized in 30% polymeric surfactant, 30% moderate-chain triglycerides, and 40% mixed partial glycerides, the drug development is much more challenging to determine.

8. Methods for Characterizing the Physicochemical Properties of LBF:

Particle Size Analysis: Particle size is a critical parameter affecting the stability, drug release, and bio-availability of LBFs. Dynamic Light Scattering (DLS), laser diffraction, electron microscopy, and atomic force microscopy (AFM) are powerful techniques that, when used together, provide a comprehensive analysis of particle properties. DLS measures the hydrodynamic size and size distribution of particles in a liquid medium, providing information on their dynamic behavior. While Laser diffraction, is well-suited for analyzing the size distribution of larger particles in both liquid and dry powder samples. Electron microscopy, which includes techniques like Transmission Electron Microscopy (TEM) and Scanning Electron Microscopy (SEM), allows for high-resolution imaging of individual

particles and reveals structural details and morphology. By combining these techniques, researchers can obtain a comprehensive understanding of the physical and structural properties of particles, enabling a more complete analysis for various applications, from materials science to biology and nanotechnology:(Kalepu et al., 2013; Shrestha et al., 2014; Lin et al., 2014; Lai et al., 2014).

Dynamic Light Scattering (DLS): DLS measures the fluctuations in intensity of scattered beam light affected by the particles Brownian motion, providing information about the size distribution of particles in a liquid suspension (Lin et al., 2014).

Laser Diffraction: This technique measures the angular distribution of scattered light to calculate the particle size distribution based on the principle of diffraction (Lin et al., 2014).

Electron Microscopy (EM): TEM and SEM allow direct visualization of LBF, providing information about their size, shape, and surface characteristics at the micro- and nano-scale ((Bootz et al., 2004, Lin et al., 2014).

1. TEM is a high-resolution imaging technique that uses a focused beam of electrons to transmit through a thin specimen, allowing for the visualization of detailed internal structures at the nanoscale. TEM provides exceptionally high magnification and resolution, enabling the observation of subcellular structures, nanoparticles, crystal lattices, and other fine details that are beyond the capabilities of optical microscopy. In TEM, the electrons interact with the specimen, and the resulting electron transmission pattern is used to create images with atomic or near-atomic resolution (Williams and Carter et al., 2009; Carlton, and Ferreira et al., 2012).
2. SEM is an imaging technique that uses a focused beam of electrons to scan the surface of a specimen. It provides detailed, high-resolution, three-dimensional images of the surface morphology and topography of various materials and biological specimens. In SEM, a beam of electrons is rastered across the specimen's surface, and detectors measure the electrons that are emitted from the specimen. This information is used to create an image that reveals surface features, including texture, roughness, and fine structures (Hall et al., 2007).

Atomic Force Microscopy (AFM): AFM provides high-resolution three-dimensional images of LBF surfaces using a fine probe scanning across the sample surface AFM is imaging and surface characterization technique used in nanoscience and nanotechnology. Unlike traditional optical microscopes, AFM doesn't rely on light. Instead, it uses a sharp probe, typically with a sharp tip at the end, to scan a sample's surface. The probe is positioned just a few angstroms above the sample, and as it moves across the surface, it measures the interaction forces (such as van der Waals and electrostatic forces) between the probe and the atoms or molecules on the sample's surface. (Lin et al., 2014).

In the ever-evolving field of lipid-based drug delivery, there are emerging techniques for evaluating LBF properties that promise to provide more detailed insights into their behavior and interactions. One such technique is the use of advanced microscopy methods, including super-resolution microscopy and confocal laser scanning microscopy, which offer higher resolution and the ability to visualize lipid-based systems in greater detail. These techniques allow researchers to directly observe the structural organization and interactions within LBFs, shedding light on drug distribution, lipid phase behavior, and potential drug crystallization. Another emerging approach is the use of computational modeling and simulation, which can

predict the behavior of LBFs and assist in the rational design of optimized formulations. These techniques are set to revolutionize the development and understanding of LBFs, offering greater precision in tailoring formulations for specific drugs and improving their overall performance (**Zhang & Ding. 2016**).

Zeta Potential Determination: Zeta potential reflects the electrical charge on the surface of particles in a colloidal system and provides insight into their stability and potential for aggregation. Common methods for zeta potential determination include (Shrestha et al., 2014,):

Electrophoretic Light Scattering (ELS): ELS measures charged particles Movement underneath an applied electric field and calculates the zeta potential based on their velocity (Lin et al., 2014).

Laser Doppler Anemometry: This technique determines the zeta potential by analyzing the frequency shift of scattered light caused by the movement of charged particles (Lin et al., 2014).

Drug Loading Efficiency Assessment: The efficiency of drug loading into LBF is crucial for optimizing therapeutic efficacy. HPLC (High-Performance Liquid Chromatography), UV-Vis (Ultraviolet-Visible) spectroscopy, and DSC (Differential Scanning Calorimetry) are three analytical techniques commonly used to assess drug loading efficiency in pharmaceutical formulations. Each method has its unique strengths and limitations in terms of accuracy and sensitivity. HPLC is highly accurate and sensitive, making it a preferred choice for quantifying drug content in complex matrices. It allows for precise measurement of drug concentrations, even at low levels, and is often used for quantitative analysis. UV-Vis spectroscopy is also accurate and sensitive, especially for drugs with chromophores that absorb UV or visible light. It is a rapid and cost-effective technique for drug quantification but may have limitations when dealing with colorless or weakly absorbing compounds. While DSC, on the other hand, is primarily used to assess the thermal behavior of drug-loaded formulations. While it can provide insights into drug interactions and stability, it may not be as precise for quantitative drug content determination as HPLC or UV-Vis. HPLC and UV-Vis are highly accurate and sensitive methods for drug loading assessment, with HPLC excelling in quantitative analysis, while DSC is more focused on thermal characteristics and may have limitations for precise quantification. The choice of method depends on the specific properties of the drug and the formulation under investigation:

High-Performance Liquid Chromatography (HPLC): HPLC is widely used to quantify the amount of drug incorporated within LBF by separating and quantifying drug molecules from the lipid matrix (Lin et al., 2014).

UV-Vis Spectroscopy: This technique measures the absorbance of a specific wavelength of light by the drug, allowing for the quantification of drug loading in LBF (Lin et al., 2014).

Differential Scanning Calorimetry (DSC): DSC processes the flow of heat associated with fluctuations in the drug physical state and lipid constituents, providing information on drug loading and interaction with lipids (Lin et al., 2014).

Drug Release Kinetics: The release profile of drugs from LBF is critical to understanding their controlled release behavior. Various methods are employed to assess drug release kinetics, including (Bankar et al., 2021):

Dissolution Testing: Dissolution tests measure the frequency and amount of drug release from LBF in simulated physiological conditions. These tests involve placing the formulation in a dissolution apparatus and measuring the drugs concentration over time (Bankar et al., 2021).

Dialysis Membrane Technique: This method involves placing the LBF formulation in a dialysis bag or membrane and submerging it in a release medium. The drug diffusion across the membrane is then quantified at specific time intervals (Bankar et al., 2021).

Franz Diffusion Cell: This setup consists of two compartments separated by a membrane, with the LBF applied to the donor compartment and the release medium in receptor compartment. The permeation of drug through the membrane is monitored over time (Bankar et al., 2021).

Stability Assessment: Stability evaluation is crucial to ensure the long-term viability and performance of LBF. Methods employed for stability assessment include (Shrestha et al., 2014):

Accelerated Stability Testing: LBF formulations are subjected to accelerated aging conditions, such as elevated temperature and humidity, to evaluate their stability over a shorter period. The physicochemical properties, drug content, and degradation products are monitored (Shrestha et al., 2014).

Freeze-Thaw Cycling: LBF formulations are subjected to multiple freeze-thaw cycles to mimic storage conditions. The impact on particle size, drug release, and physical stability is assessed (Shrestha et al., 2014).

Oxidative Stability Testing: LBF formulations are exposed to oxidative stress to evaluate their resistance to oxidation. Techniques such as lipid peroxidation assays and antioxidant capacity measurements are employed (Lai al., 2014).

Structural Analysis: Detailed structural characterization helps understand the organization and arrangement of lipid molecules within LBF. Techniques used for structural analysis include X-ray diffraction (XRD) and nuclear magnetic resonance (NMR) spectroscopy have played a crucial role in advancing LBFs by providing valuable insights into the lipid matrix and drug-lipid interactions. XRD can elucidate the crystalline structure of lipids within the formulation, offering information about the stability and organization of the lipid components. NMR spectroscopy, on the other hand, enables researchers to probe the molecular-level interactions between drugs and lipids, providing details about drug solubility, orientation, and partitioning within the lipid matrix. This structural information has led to significant improvements in LBFs in several ways. First, it has allowed for the fine-tuning of lipid composition and formulation design to optimize drug solubility, stability, and release kinetics. For example, insights from XRD can guide the selection of appropriate lipids and the determination of the ideal lipid crystalline state for a given drug. NMR spectroscopy has enabled the development of tailored lipid-drug interactions, ensuring that drugs remain in a bioavailable form within the lipid carrier. (Lin et al., 2014):

X-ray Diffraction (XRD): XRD measures the diffraction pattern of X-rays passing through a sample to determine the spatial arrangement of atoms and provide information on the crystalline or amorphous nature of the lipid matrix (Lin et al., 2014).

Nuclear Magnetic Resonance (NMR) Spectroscopy: NMR provides insights into the molecular structure and interactions within LBF by analyzing the magnetic properties of atomic nuclei. It helps in studying lipid phase behavior, drug-lipid interaction, and structural changes (Lin et al., 2014).

By utilizing these characterization methods, researchers can gain a comprehensive understanding of the physicochemical properties of LBF, leading to optimized formulation design and improved drug delivery outcomes.

9. Evaluate the influence of formulation parameters

The influence of formulation parameters on LBF, it's essential to address the challenges faced during formulation development and offer professional opinions on potential improvements for achieving high drug loading efficiency, formulation stability, and improved drug release: (Kalepu et al., 2013; Shrestha et al., 2014; Lin et al., 2014; Lai et al., 2014; Chidambaram et al., 2011).

Drug Loading Efficiency: The lipid-to-drug ratio directly impacts the drug loading efficiency in LBFs. Higher lipid-to-drug ratios generally result in increased drug encapsulation within the lipid matrix. However, there is an upper limit beyond which further increases in the lipid-to-drug ratio may not significantly enhance drug loading. It is important to strike a balance between maximizing drug loading and maintaining the stability and integrity of the lipid formulation (Lai et al., 2012; Chidambaram et al., 2011).

Drug Release Kinetics: The lipid-to-drug ratio influences the drug release kinetics from LBFs. In general, a higher lipid-to-drug ratio tends to result in slower drug release rates. This is because a larger lipid matrix can deliver a more sustained drug release, allowing for controlled release over an extended period. Conversely, a lower lipid-to-drug ratio may lead to faster drug release due to reduced lipid content and increased drug accessibility (Lai et al., 2012; Chidambaram et al., 2011).

Physicochemical Stability: The lipid-to-drug ratio plays a crucial role in maintaining the physicochemical stability of LBFs. Excessive lipid content or a high lipid-to-drug ratio may result in the formation of large lipid aggregates, leading to instability, phase separation, or precipitation of the formulation. On the other hand, a low lipid-to-drug ratio may compromise the stability of the formulation by reducing the presence of lipid-based structures necessary for encapsulation and protection of the drug (Lai et al., 2012; Chidambaram et al., 2011).

Bioavailability and Therapeutic Efficacy: The lipid-to-drug ratio affects the bioavailability and therapeutic efficacy of drugs delivered through LBF. Optimal lipid-to-drug ratios can enhance drug solubility, protect the drug from degradation, and facilitate its absorption and uptake. However, extreme lipid-to-drug ratios may negatively impact drug absorption and bioavailability. Therefore, finding the right lipid-to-drug ratio is essential to ensure optimal drug delivery and therapeutic outcomes (Lai et al., 2012; Chidambaram et al., 2011).

Physical Characteristics: The lipid-to-drug ratio influences the physical characteristics of LBF, including particle size, shape, and dispersion stability. Higher lipid-to-drug ratios tend to result in larger particle sizes, while lower ratios may lead to smaller particles. Additionally, the lipid-to-drug ratio can impact the homogeneity and uniformity of the formulation. Proper control of the lipid-to-drug ratio is essential for achieving desired particle characteristics and maintaining formulation stability (Lin et al., 2014).

10. Evaluation of lipid formulation

Methodology for *In-Vitro* dissolution testing: *In-vitro* dissolution testing of LBF is a crucial step in evaluating behaviour and performance of drug release. The succeeding is a general methodology for conducting *In-vitro* dissolution testing of LBF:

Choose an appropriate dissolution apparatus based on the specific formulation and dosage form. Commonly used apparatus includes USP apparatus I (basket), apparatus II (paddle), or apparatus IV (flow-through cell). The selection depends on the formulation type and its intended administration route. Choose a dissolution medium that mimics the physiological conditions relevant to the intended route of administration. For oral LBFs, commonly used media include simulated gastric fluid (pH 1-2) and simulated intestinal fluid (pH 6.8). Ensure the medium composition, pH, and temperature are appropriate for the specific formulation being tested. Calibrate the dissolution apparatus as per the instrument manufacturer's guidelines. Pre-wet the dissolution vessel with the dissolution medium and equilibrate it to the desired temperature (Banakar et al., 2021; Kalepu et al., 2013; Shreshta et al., 2014). 1). Sample Preparation: Prepare the LBF according to the specific formulation design. Ensure the formulation is properly dispersed or suspended in the dissolution medium. For solid LBFs, prepare appropriate aliquots or slices of the formulation. 2). Start the Dissolution Test: Place the prepared formulation (e.g., liposomes, lipid nanoparticles, solid lipid matrices) or solid lipid-based aliquots into the dissolution vessel containing the pre-warmed dissolution medium. Ensure that the formulation is uniformly distributed or suspended in the medium. 3). Sampling: At pre-schedule time intervals, withdraw samples of dissolution medium from the vessel. The frequency of sampling depends on the expected release profile of formulation. Replace each withdrawn volume with fresh equal dissolution medium volume to sustain sink conditions. 4). Sample Analysis: Analyze the withdrawn samples using appropriate analytical methods, such as HPLC, UV spectrophotometry, or other suitable techniques, to quantify the amount of drug released from the formulation. Ensure that the analytical method is validated, and proper controls and standards are used for accurate quantification. 5). Data Analysis: Calculate the percentage of drug released at each time point and plot a dissolution profile or release curve. Analyze the data to determine the release kinetics, including parameters like dissolution efficiency, release rate, or release half-life. Compare the release profile of the LBF with reference or control formulations, if applicable. 6). Documentation: Record all the relevant parameters, including the dissolution apparatus, dissolution medium, sampling time points, and any deviations or observations during the test. Document the results, calculations, and analysis for future reference.

It is important to note that the specific methodology may vary depending on the formulation and specific requirements. The methodology mentioned above provides a general guideline for *In-vitro* dissolution testing of LBF, and it should be adapted and optimized based on the specific formulation characteristics and regulatory guidelines.

***In-vivo* studies:** *In-vivo* evaluation of LBF involves studying their behavior, performance, and therapeutic efficacy in living organisms. Here are some common *In-vivo* evaluation methods for LBFs:

Pharmacokinetic Studies: Pharmacokinetic studies involve assessing the behavior of the LBF in terms of drug absorption, distribution, metabolism, and excretion (ADME) in living organisms. Animal models, such as rodents or non-human primates, are commonly used. Following the administration of the LBF (e.g., oral, intravenous, or other routes), blood samples are withdrawn at various time interval, and concentrations of drug are find out by using analytical techniques. Pharmacokinetic parameters, containing maximum plasma concentration (C_{max}), area under the curve (AUC), time to reach C_{max} (T_{max}), and elimination half-life ($t_{1/2}$), are calculated to understand the drug's pharmacokinetic profile (Zhang et al., 2021).

Tissue Distribution Studies: Tissue distribution studies help evaluate the localization and accumulation of drugs and lipid-based carriers in specific organs or tissues. Animals are administered the LBF, and after a specified time, tissues of interest are collected and analyzed for drug content. Techniques such as liquid scintillation counting, autoradiography, or imaging methods (e.g., fluorescence imaging) can be employed to determine the distribution pattern and quantify drug levels in different organs or tissues (Zhang et al., 2021).

Bioavailability and Bioequivalence Studies: Bioavailability studies compare the systemic drug exposure from a LBF to a reference formulation. Animals receive the formulations through various routes, such as oral or intravenous administration. Blood samples are collected, and drug concentrations are measured. Bioequivalence studies aim to demonstrate the similarity or equivalence of different formulations in terms of their rate and extent of drug absorption. These studies provide valuable information on the formulation's performance compared to reference formulations (Zhang et al., 2021).

Pharmacodynamic Studies: Pharmacodynamic studies assess the therapeutic effects of the LBF *in-vivo*. Animal models that mimic the disease or condition of interest are used. The formulation is administered, and specific pharmacological responses or therapeutic endpoints are evaluated. These may include tumor regression, changes in biomarkers, improvement in behavioural outcomes, or modulation of specific physiological parameters relevant to the therapeutic target. Pharmacodynamic studies help determine the formulation's effectiveness in achieving the desired therapeutic outcomes (Zhang et al., 2021).

Toxicity and Safety Assessments: Toxicity and safety evaluations are conducted to assess the potential adverse effects of LBFs. Acute toxicity studies evaluate the formulation's effects after a single high-dose administration, while subchronic and chronic toxicity studies assess repeated or prolonged exposure. Animals are monitored for changes in physiological parameters, body weight, organ histopathology, and blood chemistry. These studies provide crucial information on the formulation's safety profile and potential risks (Zhang et al., 2021).

Therapeutic Efficacy Studies: Therapeutic efficacy studies investigate the effectiveness of LBFs in treating specific diseases or conditions. Animal models that closely resemble the human disease are used, and the formulation's therapeutic outcomes are evaluated. This may involve measuring tumor size reduction, disease progression inhibition, symptom relief, or improvements in clinical endpoints. These studies help determine the formulation's therapeutic potential and guide further development (Zhang et al., 2021).

Biodistribution and Imaging Studies: Biodistribution studies involve labeling the LBFor drug payload with a radiolabel or fluorescent marker. This enables tracking and visualization of the formulation's distribution in real-time. Whole-body imaging or specific organ imaging techniques, such as positron emission tomography (PET), single-photon emission computed tomography (SPECT), or fluorescence imaging, can be employed. These studies provide insights into the localization, accumulation, and clearance of the formulation in various tissues or organs (Zhang et al., 2021; Luo et al., 2018).

It is essential to adhere to ethical guidelines and regulatory requirements when conducting *In-vivo* evaluations. These studies provide critical information on the behavior, efficacy, safety, and potential clinical translation of LBFs.

***In-vitro–In-vivo* correlation (IVIVC):** IVIVC is a scientific approach used to create a relationship in between *In-vitro* drug release from a formulation and it's *In-vivo* performance in terms of pharmacokinetics or pharmacodynamics. IVIVC shows a important role in predicting the behavior of LBF in humans based on *In-vitro* dissolution or drug release data. Here is an overview of IVIVC for LBF (Zhang et al., 2021):

IVIVC Concepts: IVIVC is based on the principle that there is a direct correlation between the amount of drug released from a formulation *In-vitro* and the drug amount to be absorbed *In-vivo*. It assumes that the rate and amount of drug release from the formulation are critical aspects influencing its *In-vivo* performance.

In-Vitro Dissolution/Release evalauaion: In-vitro dissolution or release evaluation is conducted using suitable dissolution apparatus and media that mimic physiological conditions relevant to the intended route of administration. The release profiles of the drug from the LBF are measured, and important parameters such as release kinetics, release rate, and cumulative drug release are determined.

In-vivo Studies: In-vivo studies involve administering the LBF to animals or humans, and blood samples are collected at specific time intervals. Drug concentrations in the blood are determined using appropriate analytical methods. Pharmacokinetic or pharmaco-dynamic considerations such as onset of action, AUC, Cmax, and Tmax, are calculated from the plasma concentration-time profiles.

IVIVC Development: The establishment of *In-Vitro-In-Vivo Correlation* (IVIVC) for LBFs often involves the use of statistical and mathematical models to link *In vitro* parameters with *In vivo* drug behavior. Specific models employed in IVIVC for LBFs include linear regression, multiple linear regression, and nonlinear regression. These models enable the quantification of relationships between *In-vitro* characteristics (such as dissolution profiles) and *In-vivo* pharmacokinetic parameters (e.g., area under the curve, Cmax). Mathematical approaches such as the Level A, B, or C IVIVC can be applied, depending on the complexity of the formulation and the nature of the drug. Level A is the most stringent, requiring a point-to-point relationship between *In-vitro* and *In-vivo* data. Level B and C models offer more flexibility, allowing for biopharmaceutical factors to be considered. Thus, the use of these statistical and mathematical models facilitates the development of predictive IVIVC for LBFs, contributing to more efficient drug development and ensuring the reliability of these formulations in terms of drug solubility, release, and absorption *In-vivo (*Tsume et al 2013*)*.

IVIVC Validation: IVIVC models need to be validated using additional formulations or independent data sets to ensure their robustness and predictability. The models should accurately envisage the *In-vivo* performance of LBFs based on *In-vitro* dissolution/release data.

Application and Benefits: IVIVC for LBFs provides several benefits, including reducing the need for extensive *In-vivo* studies, enabling formulation optimization, predicting *In-vivo* performance of different formulations, supporting biowaivers, and facilitating the improvement and regulatory endorsement of LBFs. IVIVC can be particularly valuable in predicting the bioequivalence of generic drug products without the need for additional animal testing. The USFDA has recognized IVIVC as a powerful tool for waiving or reducing certain bioequivalence studies, such as in vivo bioavailability or bioequivalence trials, when a strong IVIVC relationship has been established. This approach not only accelerates the generic drug approval process but also aligns with ethical concerns related to animal welfare. **Reference:** U.S. Food and Drug Administration. (2015). In Vitro-In Vivo Correlations for Lipid-Based Drug Products. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/vitro-vivo-correlations-lipid-based-drug-products

Regulatory Considerations: IVIVC has gained recognition and importance in regulatory assessments, as it helps establish a scientific basis for envisaging *In-vivo* behaviour using *In-vitro* data. Regulatory organisations, i.e US FDA and the European Medicines Agency (EMA), encourage the use of IVIVC to support formulation development and biopharmaceutical characterization.

It is essential to developing a robust IVIVC for LBFs requires careful consideration of formulation characteristics, release mechanisms, and the complexity of *In-vivo* behavior. The establishment and validation of IVIVC models for LBFs contribute to efficient formulation development, reduced costs, and improved drug product quality (Zhang et al., 2021).

11. Summary and Future Prospectives

Lipid-containing formulations have gained significant attention in the arena of drug delivery because of their aptitude to improve drug solubility, improve bioavailability, and target specific sites of action. These formulations typically consist of lipids, surfactants, and co-surfactants that self-assemble into various structures such as micelles, liposomes, or nanoemulsions. The physical and chemical properties of LBFs, with particle size, zeta potential, surface morphology, and drug loading efficiency, can be characterized using various analytical techniques. The choice of lipid components, such as phospholipids, surfactants, and co-surfactants, shows an important role in determining the properties and performance of LBFs. Different lipid components can influence drug solubilization, stability, drug release kinetics, and interactions with biological membranes. Understanding the impact of lipid components is crucial for optimizing the formulation and achieving the desired therapeutic effect. Formulation parameters, such as the lipid-to-drug ratio, also have a noteworthy impact on the stability and performance of LBFs. Optimizing the lipid-to-drug ratio can ensure efficient drug encapsulation, controlled drug release, and enhanced stability during storage and administration. Additionally, the choice of manufacturing techniques and process parameters can influence the quality and performance of LBFs.

In-vitro evaluation methods, including drug release studies and dissolution testing, provide insights into the release kinetics and dissolution behavior of LBFs. These studies help assess

the formulation's drug release profile, dissolution rate, and potential drug interactions. *In-vivo* evaluation involves studying the behavior, pharmacokinetics, pharmacodynamics, tissue distribution, and therapeutic efficacy of LBFs in living organisms. *In-vivo* studies provide crucial information on the formulation's performance, safety, and efficacy in relevant animal models or human subjects.

Additionally, a number of patents have also been submitted and granted. **Table 4** summarizes the brief features of these, which illustrate diverse formulation elements and the potential of LBFs.

Future Prospects: The field of lipid-containing formulations holds significant promise for the growth of advanced or novel drug delivery systems. Emerging technologies in LBFs hold great promise for future developments in pharmaceutical formulations. One noteworthy area of innovation is the utilization of lipid-based nanoparticles, such as NLCs and lipid-drug conjugates. NLCs provide enhanced drug loading, controlled release, and improved stability. Lipid-drug conjugates allow for efficient drug delivery and controlled release through covalent bonding, reducing the risk of premature drug degradation. Additionally, lipid-coated dosage forms, including lipid-coated tablets and nanoparticles, offer novel strategies to optimize drug delivery, enabling tailored release profiles and improved solubility. The advancement of lipidomics and artificial intelligence in formulation design allows for a more personalized approach to drug delivery, tailoring LBFs to individual patient needs. Moreover, the development of intelligent lipid nanocarriers that respond to specific physiological cues, such as changes in pH or enzyme levels, promises more precise drug targeting. These emerging technologies collectively open doors for innovative pharmaceutical formulations that enhance drug bioavailability, stability, and therapeutic efficacy, paving the way for the future of lipid-based drug delivery. Future research and development efforts are expected to focus on the following aspects:

Targeted Delivery Systems: The incorporation of targeting ligands or stimuli-responsive components into LBFs can enable site-specific drug delivery and enhance therapeutic efficacy while minimizing off-target effects.

Combination Therapies: LBFs offer opportunities for combining multiple drugs or therapeutic agents into a single formulation. This approach can enhance synergistic effect to improve therapeutic outcomes, and simplify treatment regimens.

Personalized Medicine: Advancements in LBF technologies may enable personalized medicine approaches by tailoring drug delivery systems to individual patient needs, taking into account factors such as genetic profiles, disease characteristics, and patient-specific requirements.

Nanotechnology and Lipid-Based Systems: Integration of nanotechnology with lipid-based systems, such as lipid nanoparticles or liposomal formulations, can provide enhanced drug delivery capabilities, improved stability, and controlled release profiles.

Biocompatibility and Safety: Further research is needed to address concerns related to the biocompatibility and long-term safety of LBFs, including potential toxicity, immune responses, and biodistribution.

Scale-up and Manufacturing: Development of scalable manufacturing processes for LBFs is crucial to ensure cost-effective production and commercialization of these delivery systems.

Regulatory Considerations: As LBFs continue to advance, regulatory guidelines and standards need to be established to ensure their quality, safety, and efficacy. This includes guidelines for characterization, stability testing, and IVIVC.

12. Conclusion:

In conclusion, LBFs have demonstrated significant potential in improving the bioavailability of lipophilic drugs. Lipophilic drugs often face challenges related to their poor aqueous solubility, limited absorption, and low bioavailability. LBFs provide a promising approach to overcome these limitations and enhance drug delivery.

By incorporating lipids, surfactants, and co-surfactants, LBFs can form various self-assembled structures, such as micelles, liposomes, or nanoemulsions. These structures offer several advantages for lipophilic drug delivery, including improved drug solubility, enhanced drug stability, and protection against degradation. The ability of lipids to dissolve and solubilize lipophilic drugs enhances their bioavailability by facilitating their absorption and systemic circulation. Moreover, LBFs can improve drug release kinetics and control the release rate of lipophilic drugs. This allows for sustained and controlled drug release, leading to prolonged drug exposure and improved therapeutic outcomes. The lipid components in these formulations can also interact with biological membranes, promoting cellular uptake and enhancing drug permeation. Additionally, LBFs offer the potential for targeted drug delivery and site-specific action. Through surface modification or the incorporation of targeting ligands, these formulations can enhance drug accumulation at specific disease sites, minimizing off-target effects and maximizing therapeutic efficacy. The improvement in LBFs has been supported by advances in formulation technologies, characterization techniques, and manufacturing processes. However, further research is needed to optimize these formulations, establish robust IVIVC, ensure long-term safety, and address regulatory considerations. Overall, LBFs hold great potential in improving the bioavailability of lipophilic drugs candidates, addressing formulation challenges, and enhancing therapeutic outcomes. With continued research and development, LBFs have the potential to revolutionize the delivery of lipophilic drugs and improve patient care. However, their inherent capacity to increase the bioavailability of lipophilic medications with limited water solubility, lipid carriers have a bright future.

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Table: 4 Patent reports examples for lipid containing formulation

S.No	Patent Application No.	Drug Molecule and Formulation System	Inventor(s)	Ref. No	Invention
1.	US5993858A	----	*Crison, John R. Amidon, Gordon L*	Crison et al., 1999	This invention provides a self-microemulsifying the excipient composition for enhancing medication bioavailability
2.	US5858401A	Cyclosporine	*Bhalani, Vinayak T Patel, Satishchandra P*	*Bhalani et al.*, 1999	The invention creating a drug delivery system for enhancing a drug's bioavailability by emulsifying at least one drug with a self-microemulsifying excipient composed of an oil or other lipid material.
3.	WO2015/059466A1	Efavirenz	*Malhotra, Geena Purandare, ShrinivasM*	Malhotra et al., 2015	A pharmaceutical composition containing efavirenz and one or more pharmaceutically acceptable excipients, with the self-

					emulsifying drug delivery system comprising efavirenz and one or more pharmaceutically acceptable excipients
4.	WO2014009434A1	Abiraterone or abiraterone acetate	*Legen, Igor Peternel, Luka* *Novak, Stagoj Mateja Homar, Miha Rozman, Peterka Tanja* *Klancar, Uros*	Legen et al, 2014	The invention additionally provides a technique for producing SMEDDS and a pharmaceutical formulation incorporating SMEDDS.
5	WO2015142307A1	Rosuvastatin	*Karasulu, H. Yesim Apaydin, Sebnem Gundogdu, Evren Yildirim, Simsir Llgin Turk, Ugur Onsel Karasulu, Ercument Yilmaz, Candeger Turgay, Tugce*	*Karasulu* et al., 2015	The investigation highlighted the possible function of SMEDDS in increasing bioavailability as well as the therapeutic potential of the HMG-CoA reductase inhibitor rosuvastatin
6.	US20140017308A1	Statin	*Hustvedt, Svein Olaf Berge, Gunnar, Olesen, Preben Houl-*	*Hustvedt* et al., 2014	There are descriptions of compositions and uses that contain a fatty acid oil

			berg *Müllertz, Anette*		combination. that can produce SNEDDS, SMEDDS, or SEDDS in an aqueous solution.
7	WO2013100869A3	LyP-1 peptide (CGNKRTRGC)	*Reyhan, Neslihan Gursoy* *Ozge, Çevik*	Reyhan et al., 2014	For cancer treatment or imaging, the invention is a system of nanocarrier composition consisting of a SMEDDS
8.	US20070104740A1	HIV protease inhibitor	*Voorspoels, Jody Firmin*	Voorspoels et al.,2007	The invention pertains to pharmacological formulations of (3R,3aS,6aR)-hexahydrofuro[2,3-b]. furan-3-yl(1S,2R)-3-[[(4-aminophenyl) sulfonyl](isobutyl) amino]-1-benzylSMEDDS including a lipophilic phase, one or more surfactants, a hydrophilic solvent, and a nucleation inhibitor.

9.	US20050232952A1		*Lambert, Gregory Razafindratsita, Alain Garrigue, Jean-Sebastien* *Yang, Shicheng Gursoy, Neslihan Benita, Simon*	Lambert et al., 2005	The invention is a pharmaceutical SMEDDS that contains one or more therapeutic agent(s) with low water solubility or that are water insoluble, vitamin E.
10.	US20060275358A1	Coenzyme Q10	*Lin Jing*	Lin 2012,	The present invention includes a SMEDDS in the form of a mixture constituted of a hydrophilic surfactant and a lipophilic cosurfactant (forming a surfactant pair). The compositions were extremely soluble and stable in storage.
11.	WO2002007712A2		*Ping Gao, Walter Morozowich, Narmada S.*	Gao et al., 2002	A formulation for administering an extremely water-insoluble active component is described.
12.	EP2790683A2	LyP-1 peptide (CGNKRTRGC)	*Gursoy, Reyhan Neslihan Cevik, Ozge*	Gursoy and ozge 2014	This invention involves the formulation

					of LyP-1 peptide in SMEDDS, which was acquired from MDA MB-435 cells via phage display and has the amino acid sequence CGNKRTRGC.
13.	US8536208B2	Antifungal active com-pound (I) wherein R1, R2 and R3 are indepen-dently of one another hydrogen, F or Cl.	*Bucher, Christian Ditzinger, Guenter Dubois, Estelle Marchaud, Delphine*	Bucher et al., 2013	A pharmaceutical composition for oral administration that self-emulsifies when it comes into contact with an aqueous phase, particularly GI fluids
14.	US8790723B2	Ubiquinone (CoQ10)	*Khan Mansoor A Nazzal, Sami*	Khan and Nazzal 2014	SNEDDS of poorly water-soluble medication, such as ubiquinone (CoQ10), is preferable for pharmacological efficacy. The SNEDDS can then be combined with a powder to create a solid dose form.

15	US7736666B2	---	*Holmberg, Christina Siekmann, Britta*	Holmberg et al., 2010	This invention claims and reveals a pharmaceutical composition that is appropriate for oral administration as a form of an emulsion pre-concentrate
16	US7226932B2	---	*Rajeev Gokhale, Martin J. Griffin, James E. Truelove, James C. Stolzenbach, Aziz Karim, Ajit, K. Roy*	Gokhale et al., 2007	It is described an oral pharmaceutical formulation that enhances the bioavailability of medications that are significantly water and oil insoluble
17	US8835509B2	Curcumin	*Kanchan Kohli, Sunny Chopra, Saurabh Arora, Roop K. Khar, Kolappa K. Pillai*	Kohli et al 2014	The current invention describes a pharmaceutical composition consisting of curcuminoids in the form of a SNEDDS formulation.
18	CA2674128A1	---	*Igor Legen Janez Kerc Polona*	Igor et al., 2008	SMEDDS and microemulsions that contain a

			Jurkovic		polyoxyethylene sorbitan fatty acid ester emulsifier, a fatty acid ester co-emulsifier, and an oil to improve the solubility
19	US20120095075A1	---	*Muthiah Manoharan,* *Kallanthottathil G. Rajeev,* *David Butler,* *Narayanannair K. ,Jayaprakash,* *Muthusamy Jayaraman,* *Laxman Eltepu.*	Manoharan et al 2012	The present invention provides lipids that are advantageously used in lipid particles for the *In-vivo* delivery of therapeutic agents to cells.
20	AU2022204907A1	--	*Frank Derosa,* *Braydon Charles Guild,* *Michael W. Heartlein.*	Derosa et al., 2022	Novel lipids and liposomal compositions made using such substances, as well as associated techniques of neutralizing or otherwise changing such liposomal

					compositions, are disclosed herein. The lipids disclosed herein can be used as liposomal carriers to assist the delivery of encapsulated polynucleotides to target cells and subsequent transfection of those cells. In other implementations, one or more of the chemicals that form the liposomal delivery vehicle are neutralized or further changed, resulting in changes to the liposomal delivery vehicle's characteristics.
21	CA3003055C	Nucleic acid	*Steven M. Ansell* *Xinyao Du*	Ansell et al., 2023	The current invention includes cationic lipids and lipid particles made up of these lipids that are useful

					for *In-vivo* nucleic acid delivery, as well as nucleic acid-lipid particle compositions appropriate for *In-vivo* therapeutic usage.

*DDS- Drug Delivery System, SNEDDS: self-nanoemulsifying drug delivery systems, SMEDS: self-microemulsifying drug delivery systems, SEDDS: self-emulsifying drug delivery systems