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Development And Evaluation Of Lipid-Based Formulation For Improvement Of Bioavailability

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ABSTRACT

The principal objective of formulation of lipid-based drugs is to enhance their bioavailability. The use of lipids in drug delivery is no more a new trend now but is still the promising concept. Lipid-based drug delivery systems (LBDDS) are one of the emerging technologies designed to address challenges like the solubility and bioavailability of poorly water-soluble drugs. This paper mainly focuses on novel lipid-based formulations, namely, emulsions, vesicular systems, and lipid particulate systems and their subcategories as well as on their prominent applications in pharmaceutical drug delivery. This chapter aims to illustrate the mechanisms by which lipid-based formulation (LBF) overcome bioavailability limitations and control drug release, rationalize the formulation design, describe methods for characterization and identification of critical quality attributes, and explore their emerging applications including modified release formulations.In this paper we will discuss. Development and Evaluation of lipid-based formulation for improvement of bioavailability.

Keywords:

Development, Evaluation, Lipid-Based Formulation, Improvement, Bioavailability, Drug Delivery Systems, Poorly Water-Soluble Drugs, Semi-Solids, Gastrointestinal, Solubility, Mixed Micelles.

Introduction:

Lipid-based formulations encompass a wide variety of delivery modes and technologies, ranging from immediate release to sustained release formulations, from liquids to semi-solids, from crystalline suspensions to lipid solutions, from systems containing small-molecule active pharmaceutical ingredients (APIs) to those containing more complex peptide-based molecules, and finally from those intended for oral administrations through to topicals and parenteral. [1]

The flexibility of lipid formulation technologies provides the potential to modify pharmaceutical properties such as stability and ease of manufacture, and pharmacokinetic properties such as enhanced absorption and bioavailability, sustained exposure and targeted delivery. With the exception of liposomal technologies (that represent a class of delivery system in their own right

and have not been considered here), much of the interest in lipid-based formulations has focused on their use to enhance the oral bioavailability of poorly water-soluble drugs. Drugs with low water solubility continue to present a formidable challenge to effective drug development and commonly show poor, variable, and food-dependent absorption and bioavailability after oral administration. [2]

Several strategies that enable effective delivery of poorly water-soluble compounds are apparent and, in general, may be stratified as technologies that modify solute-solute interactions in the solid state, that enhance solute-solvent interactions in solution, that promote dissolution via changes in surface area, or combinations of the three approaches. Formulation technologies to enhance solubility and dissolution rate include salt formulation, modification of crystal form (amorphous, cocrystals, polymorphs), particle size reduction/nano milling, alteration of solution/solubilization conditions (cosolvents, surfactants, cyclodextrins etc.), and approaches such as solid dispersions and lipid-based formulations that may, in practice, achieve a number of these goals.

Evaluation of the Utility of Lipid-Based Formulations:

Assess two self-emulsifying formulations of amiodarone and talinolol in rats and show significant increases in bioavailability in both cases after administration of the lipid formulation. Subsequent studies suggest that the lipid formulation leads to increases in gastrointestinal (GI) solubilization and absorptive permeability, and in the case of talinolol in particular, possible effects on P-glycoprotein efflux.

Explore the potential for lipid-based formulations of cinnarizine to promote drug absorption via the induction of supersaturation at the absorptive membrane. Using a series of in situ intestinal perfusion and bioavailability studies, the authors show that lipid absorption from intestinal mixed micelles at the absorptive membrane is likely to reduce micellar solubilization capacity, promote supersaturation, and drive increases in drug absorption. [3]

The data therefore suggest that formulations containing absorbable lipids may provide inherent advantage in the promotion of supersaturation and, as a result, in enhancing the absorption of poorly water-soluble drug cargoes.

Lipid Based Drug Delivery:

One of the popular and recent approaches to improve the oral bioavailability of poorly water-soluble compounds are lipid-based formulations in which the drug compounds are incorporated into inert lipid vehicles such as oils and surfactant dispersions, self-emulsifying drug formulations and emulsions.

- Self-dispersing solid (solution with surfactants): The stearic hindrance to aggregation may build into product and the physical stability of the product is questionable as the drug or polymer may crystallize.
- Lipid solution (LFCS Type I): These are effective for lipophilic drugs and drug is presented in solution avoiding the dissolution step.
- Self-emulsifying drug delivery system (LCFS Type II or Type III lipid systems): It is an effective method to incorporate the drug into self- emulsifying liquid whereby emulsification forms an o/w emulsion spontaneously on mixing with water. For such formulations dispersion leads to rapid absorption and absorption is independent on digestion.

- Solid or semi-solid SEDDS: They are prepared as a free-flowing powder or compressed into a tablet form. The surfactant used may be poorly tolerated in chronic use and physical stability of the product is questionable as drug or polymer may crystallize.
- Surfactant-cosolvent systems (LCFS Type IV lipid systems): These formulations have the relatively high solvent capacity for typical APIs. The surfactant used may be poorly tolerated in chronic use. There is the significant threat of drug precipitation on dilution. [4]

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. [5]

Main factors affecting the choice of excipients for lipid-based formulations are as follows:

1. Solubility,
2. Dispersion,
3. Digestion,
4. Absorption.

Formulation approaches of lipid-based drug delivery system:

By considering the formulation objectives of the lipid-based drug delivery system can be developed successfully. The names of commercially available lipid-based drugs are tabulated in table. There are various approaches for the lipid-based drug delivery system which are discussed below.

- **Oily liquids:** Highly lipophilic drugs (e.g. steroids) are soluble in oil only, so these drugs have to be formulated as oily liquids. An oily solution of bupivacaine, a free base was prepared by using a mixture of fractioned coconut oil (viscoleo®) and coconut oil.
- **Mixed micelles:** The systems resemble a lipid bilayer which is a disc-like structure. In detergent-lipid mixed micelle, the lipid molecule is shielded by detergent to protect against water on the surface. The activity of paclitaxel and parthenolide was reported to be increased against taxol-resistant and sensitive lung cancer cell line when co-encapsulated in mixed micelle of PEG 2000 - distearyl phosphatidylethanolamine (DSPE) and Vitamin E TPGS.
- **Self-emulsifying system:** Due to the presence of different surfactants in the oily phase, the system can emulsify. The lipophilic drug is solubilized in the oil phase and surfactants used help in the dispersion of the oily phase in GI fluid. The formulation of a self-emulsifying system is generally composed of the drug, oily vehicle, surfactant, co-surfactant, and co-solvent. It was reported that SMEDDS sustained-release pellets of puerarin were formulated using castor oil as oil phase, Cremophor®EL as an emulsifier, and 1,2-propanediol as the co-emulsifier for oral administration.

- Liposomes: Liposomes are spherical bilayer which adequately reflects the cell membrane in their structural arrangement. Phospholipids that are being amphiphilic are used in liposomes ormation. These phospholipids when undergo hydration in water forms spherical bilayer structure. Because of the unique formation of this complex structure, hydrophilic substances can be embedded into the aqueous internal space of the globule whereas hydrophobic drugs can be solubilized within the inner fatty acid layer. Propylene glycol liposomes loaded with epirubicin having enhanced permeability to both the healthy cell membrane and nuclear membrane of the tumor cell is reported to overcome multidrug resistance in Breast cancer. [6]

Problems associated with methods used for improvement of bioavailability:

The improvement of solubility of hydrophobic drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate, there are practical limitations for these techniques. The salt formation is not feasible for neutral compounds and the synthesis of appropriate salt forms of drugs that are weakly acidic or weakly basic may often not be practical. [7]

The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization. Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of improper handling and wetting3. To prevail over these limitations, various formulation methods are available like addition of cyclodextrins and permeation enhancers and preparation of nanoparticles and solid dispersions. [8]

Review of Literature:

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). [9]

(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. [10]

In the formulation of LBDDS, compound with low water solubility, specifically, those in BCS class II and IV, are frequently considered. Different physical and chemical factors might lead compounds

to fall between BCS II and IV; as a result, figuring out the reason for the low solubility could be important. Because of their rigid crystal structure, poorly water-soluble compounds are known as "brick dust" and cannot be synthesized as LBDDS. Another class of compounds, known as "grease-balls," has a high lipophilicity (log P) and significantly lower melting temperatures. Between these two simplified classifications of poorly soluble compounds, there is undoubtedly a spectrum, with most therapeutic molecules sitting somewhere in the middle. If a chemical has grease-ball characteristics and standard formulation techniques do not produce the desired bioavailability, it may be advantageous to increase solubility by adding surfactants and/or lipid-based excipients. The solubility of a substance, if it is a "brick-dust" molecule, is often constrained in lipids, but it may be considerably boosted in surfactants and co-solvents. Because of this, not all substances with poor water solubility and/or an elevated log P will have good solubility for excipients utilized in LBDDS (Mu et al., 2013). [11]

Objectives:

- Development and Evaluation of Lipid-Based Formulation for Improvement of Bioavailability.
- Lipid-based formulations are designed to address the challenge of poor solubility by enhancing the drug's solubility in lipids, making it more bioavailable.
- Problems associated with methods used for improvement of bioavailability.
- Developing successful lipid-based formulations

Research Methodology:

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.This chapter aims to illustrate the mechanisms by which lipid-based formulation (LBF) overcome bioavailability limitations and control drug release, rationalize the formulation design, describe methods for characterization and identification of critical quality attributes, and explore their emerging applications including modified release formulations. In this paper we will discuss. Development and Evaluation of lipid-based formulation for improvement of bioavailability.

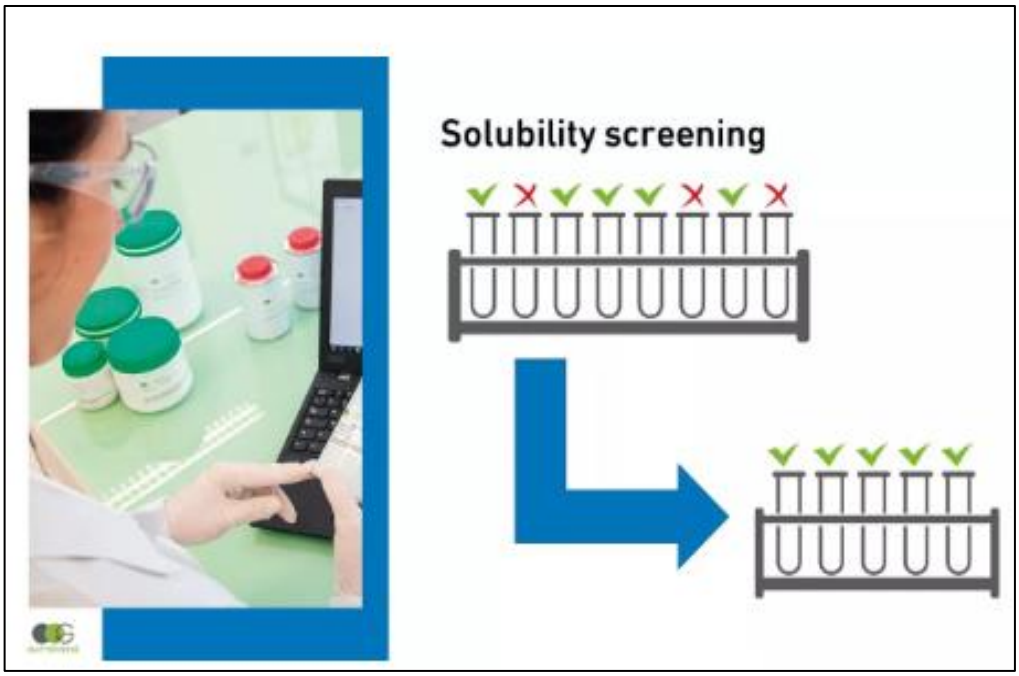
Result and Discussion:

Developing successful lipid-based formulations step by step:

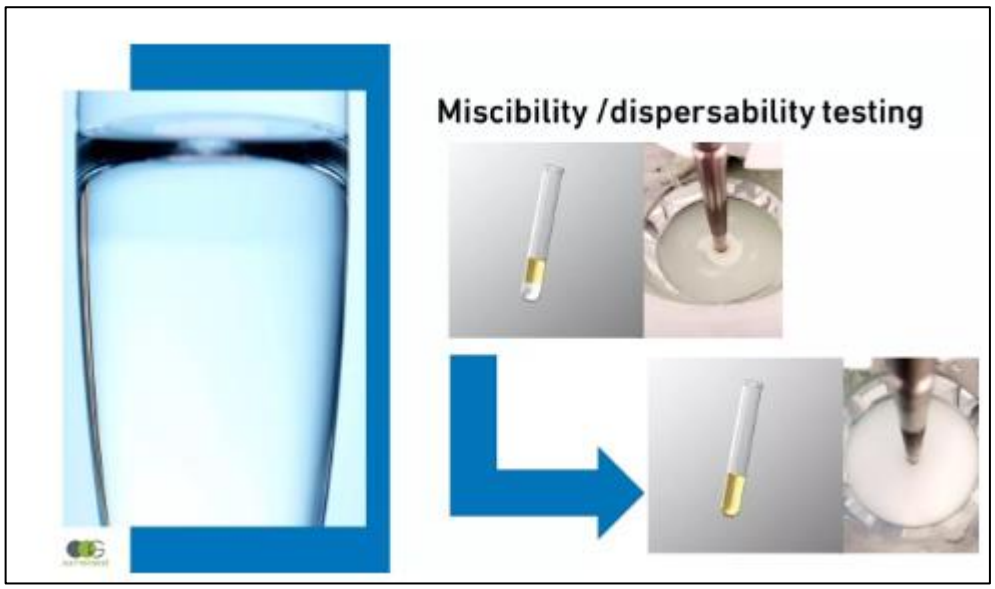
Lipid-based formulations are a powerful tool to increase oral bioavailability of poorly water-soluble or poorly permeable drugs. They can be used from early-stage development to market, significantly reducing the development time. Consisting in a mixture of excipients they are easy to formulate, scale-up and produce.

An optimized lipid-based formulation enables solubilization of the entire therapeutic dose and maintains the drug in solubilized state throughout the digestion process. It is developed in 3 key steps:

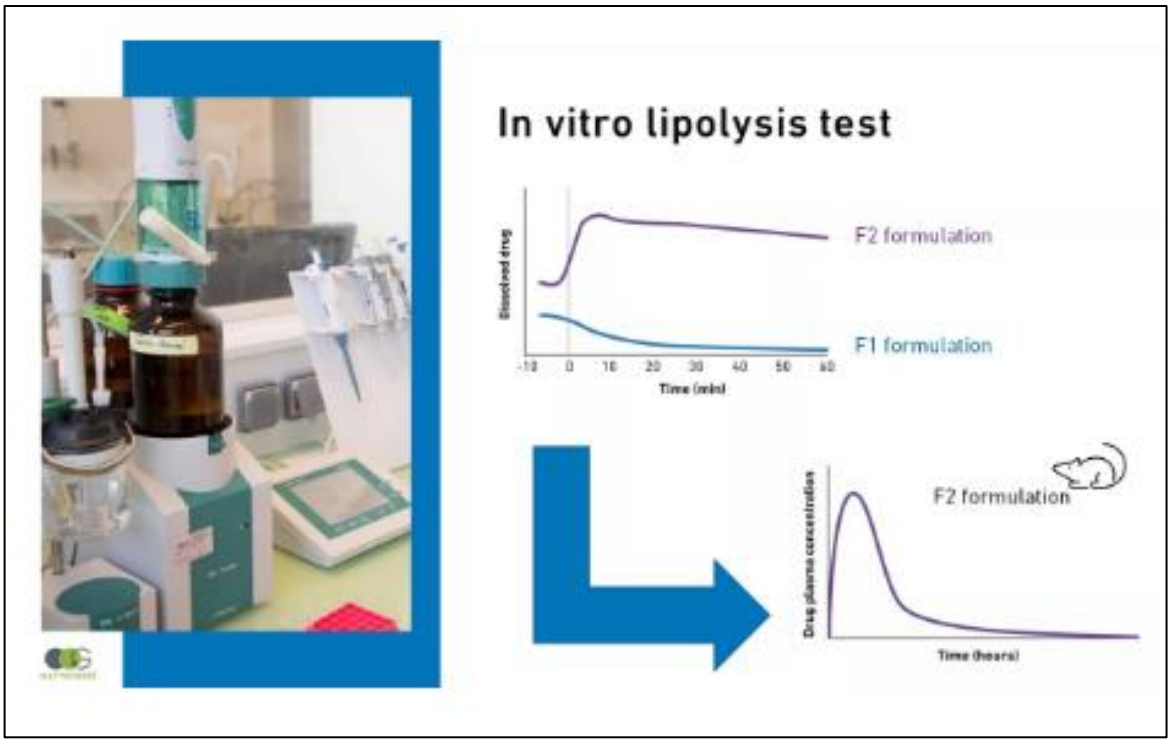
First, measure the saturation solubility of your drug in a range of excipients: oils, surfactants, and solvents.



Second, test the miscibility of binary mixtures of excipients and their dispersibility in water. Select excipients that are miscible and dispersible in aqueous solution.



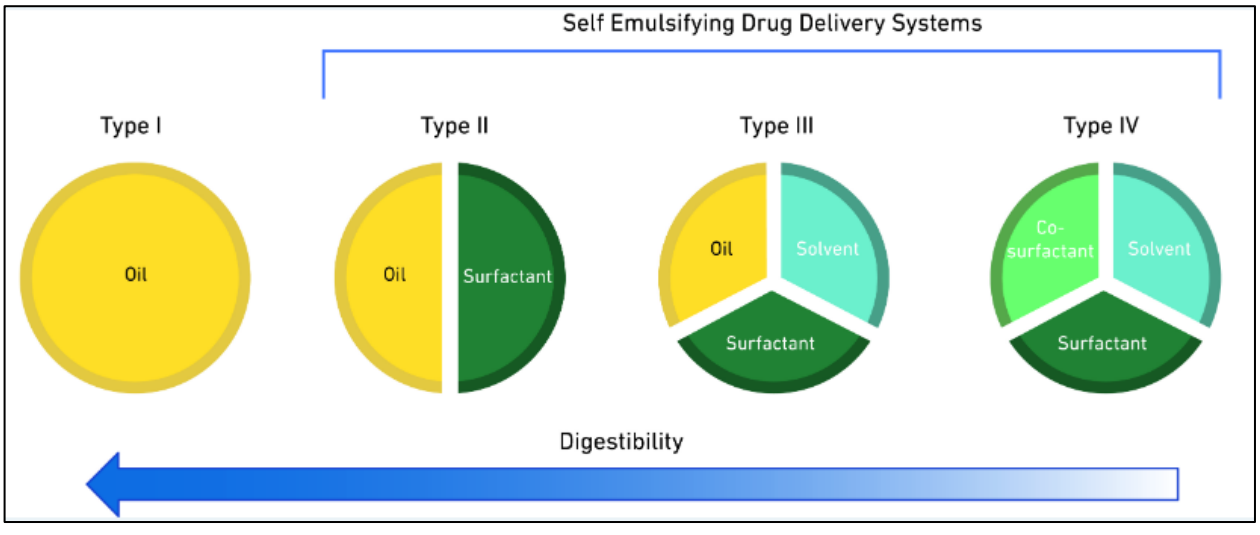
Third, perform the in vitro digestion test to evaluate the ability of the formulation to maintain the drug in solubilized state throughout the digestion test.



The literature on lipid-based formulations is abundant and many different words are used to describe lipid-based formulations. Let's explore them and understand the similarity and differences.

Self-emulsifying lipid formulations, or self-emulsifying drug delivery systems, form emulsions upon contact with aqueous fluids without the need for mechanical or thermal energy. The size of the dispersion depends on the composition of excipients in the formulation:

SMEDDS: self-micro emulsifying drug delivery systems



LFCS: Lipid Formulation Classification System is used to facilitate the identification of the lipid-based formulations, based on the composition, the size of the droplets generated after the dispersion of the formulation in aqueous media, and the impact of natural lipid digestion process on the in vivo performance of the formulation classes (Type I, II, III or IV). [12]

Lipid Formulation Classification System:

The lipid formulation classification system (LFC) was introduced as a working model in 2000 and an extra "type" of formulation was added in 2006. In recent years the LFCs have been discussed more widely within the pharmaceutical industry to seek a consensus which can be adopted as a framework for comparing the performance of lipid-based formulations. The main purpose of the LFCs is to enable in vivo studies to be interpreted more readily and subsequently to facilitate the identification of the most appropriate formulations for specific drugs, that is, with reference to their physiochemical properties as depicted in Table 1. Table 1 shows the various classes of LFCS. Most of the marketed products are Type III systems, which are diverse with a wide range of oil- and water-soluble substances. Hence, this group has been further divided into Type III A (oils) and Type III B (water-soluble) based on the proportion of oils and water-soluble substances. [13]

Table 1: The lipid formulation classification system. [14]

Type I	Type II	Type IIIA (Fine emulsion)	Type IIIB (micro emulsion)	Type IV
Oils without surfactants	Oils and water insoluble surfactants	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	Water-soluble surfactants and cosolvents (no oils)
Non-dispersing	Emulsion (SEDDS)	SEDDS/SMEDDS formed with water-soluble components	SEDDS/SMEDDS formed with water-soluble components and low oil content	Disperses typically to form a micellar solution
Requires digestion	Will be digested	Digestion may not be necessary	Digestion may not be necessary	Limited digestion

Formulation Approaches:

Lipid-based drug delivery systems can be developed successfully by careful consideration of the formulation objectives. Table 2 indicates the list of commercially available lipid-based products. The systematic approach includes pre-selection of excipients based on their melting point, fatty acid composition, HLB value, digestibility and disposability; screening of selected excipients for solubility, dissolution/dispersion properties, stability and compatibility; identification of a formulation technique which is suitable for the intended dosage form; design of appropriate animal models to predict the in vivo performance of the chosen formulation; and optimization of the formulation considering the drug loading and dissolution profile. [15]

Table 2. Commercially available Lipid-based products for oral administration

Trade Name	Molecule	Therapeutic use	Company
Agenerase	Amprenavir	HIV antiviral	Glaxo SmithKline
Rocaltrol	Calcitriol	Calcium regulator	Roche
Cipro	Ciprofloxacin	Antibiotic	Bayer
Neural	Cyclosporine A/I	Immuno-suppressant	Novartis
Gengraf	Cyclosporine A/III	Immuno-suppressant	Abott
Accutane	Isotretinoin	Anti-comedogenic	Roche
Kaletra	Lopinavir and Ritonavir	HIV antiviral	Abott
Norvir	Ritonavir	HIV antiviral	Abott
Lamprene	Clafazamine	Treatment of Leprosy	Alliance laboratories

Trade Name	Molecule	Therapeutic use	Company
Sustiva	Efavirensz	HIV antiviral	Bristol-Meyers
Fenogal	Finofibrate	Anti hyperlipproteinomic	Genus
Restandol	Testosterone undercanoate	Hormone replacement therapy	Organon laboratories
Convulex	Valproic acid	Anti-epileptic	Pharmacia
Juvela	Tocopherolnicontinate	Hypertension, hyperlipidemic	Eisai Co.

Tentativedrugcandidatesselectedfororallipid-based formulations:

BCS which isrelated with bioavailability. The lipid-based formulations which are depicted in Table 3 can potentially improve bioavailability for selected compounds in every BCS category. The BCS CategoryII compounds possessing poor water solubilityand highmembranepermeabilityexhibit substantialenhancements inbioavailabilitywhen formulated in solubilizing lipid excipient.

Although these compounds are hydrophobic, they possess solubility (50-100mg/ml) in a dietarytriglyceride in which drugs can be dispersed and enhances bioavailability by overcoming absorptivebarriers of poor aqueous solubility and slow dissolution in the gastrointestinal tract. The enhanced absorption of hydrophobic molecules through lipid formulations involves a mechanism of transfer into the bile salt-mixed micellar phase in which the absorption occurs readily across the intestinal epithelium.

The process depends on the oil nature, surfactant concentration and the oil/surfactant ratio and the temperature at which the self- emulsification occurs. For selected compounds under BCS category of lipid-based formulations can potentially enhance bioavailability which is illustrated in Table 3.

The typical composition of various types of lipid formulations according to Lipid formulation classification system LFCS is indicated in Table 4.

Table 3: Potential bioavailability improvement of active ingredients categorized by the Biopharmaceutical classification system using oral lipid-basedformulations: [16]

Aqueous Solubility	Membrane permeability	Type[1]	Potential formulation Type	Potentialbenefitsofthe system
High	High	I	Microemulsion w/o	Stabilization,chemical enzymatic protection against hydrolysis (+efflux).
High	Low	III	Microemulsion w/o	Stabilization,chemical enzymatic protection against hydrolysis (+efflux).
Low	High	II	Self-micro emulsifyingdrug delivery system (SMEDDS) o/w	Enhancement of dissolution, solubilization, and improved bioavailability
Low	Low	IV	Self-micro emulsifyingdrug delivery system (SMEDDS) o/w	Enhancement of dissolution,solubilization and improved bioavailability(+efflux).

Lipid-based Drug Delivery: Classification System:

Lipid-based formulation implies different systems including solutions, emulsions, micellar systems, self-emulsifying drug delivery systems and self-micro emulsifying drug delivery systems.

A lipid classification system as mention in table 1 which classified different formulation into four classes. [17]

Table No. 4: Lipid Formulation Classification System:

Typesofexcipientsin formulation	Percentagecontentofformulationinweightbasis				
	TypeI	TypeII	TypeIIIA	TypeIIIB	TypeIV
Triglyceridesormixed monoanddiglycerides	100	40-80	40-80	<20	-
Waterinsoluble Surfactants(HLB< 12)	- -	20-60	- -	- -	0-20
Watersolublesurfactants (HLB>12)	- -	- -	20-40	20-50	30-80
Cosolvents(Hydrophilic) (e.g.PEG,propylene, transcutol)	- -	- -	0-40	20-50	0-50

Table No. 5: Characteristics of different type of lipid classes classified by the lipid classification system [18]:

Types/characteristics	Dispersibility	Digestibility	Initial solvent capacity	Solvent capacity upon dispersion	Solvent capacity upon digestion
I	Pure oil Limited or no dispersion	Digestible	Poor	Bo impact	Increased
II	SEDDS* Mild dispersion with the absence of hydrophilic components	Probably to be digestible	Intermediate	No Impact	Possible Loss
IIIA	SMEDDS** Fast dispersion in presence of hydrophilic components to form micro-nanoemulsion	Maybe digestible	Slightly above intermediate	Possible loss	Possible loss
IIIB	SMEDDS Very fast dispersion in presence of hydrophilic and low oil to form micro/nanoemusion	Poorly digestible	High	Possible loss	Possible loss
IV	Oil-free Rapid dispersion forming a micellar solution	Not digestible	High	Likely loss	No impact

(*SEDDS = Self emulsifying Drug delivery system, **SMEDDS= Self micro emulsifying drug delivery system)

Different types of lipid classes have different properties as mentioned in table 5. Type I lipid-based formulation contains oils like triglycerides or a mixture of di and monoglycerides which must be digested to facilitate the drug absorption within the gastrointestinal tract. Type I formulation is simple and biocompatible which shows that they are safe listed excipient.
In the case of type, I formulation lipid digestion makes not lose the solubilization capacity after dispersion and digestion. This indicates that there are no possibilities of precipitation and loss of bioavailability. Type II lipid-based formulation is composed of a mixture of lipids and water-insoluble surfactants (HLB12) and cosolvents. When these formulations come in contact with gastrointestinal fluids, they undergo self-emulsification (i.e. SEDDS when the system is milky emulsion) having the droplet size greater than 200 nm or SMEDDS when a transparent emulsion is formed with less globular size.
The type IV formulations do not contain oil which is based on water-soluble surfactants and co-solvents. When these components get dispersed in the aqueous medium then fine dispersions are formed which leads to rapid drug release and absorption. Hence, during dispersion, there is a risk of precipitation in the gastrointestinal tract. [19]

Characterization of Lipid-based Drug Delivery System:

a. Physical analysis:

The thermal behavior of the lipid's during formulation is changed because lipid excipients have a complex chemical composition which tends to broad melting ranges. Various thermal properties of lipids such as melting point, crystallization temperature, glass transition temperature, an exact determination of the solid fat content of the excipient versus temperature can be estimated using differential scanning calorimetry (DSC). X-ray diffraction (XRD) determines the crystallinity of a lipid excipient.

b. Chemical analysis:

The exact composition of the ethers, esters, and fatty acid is evaluated by Gas Chromatography (GC) and High-Performance Liquid Chromatography (HPLC). The molecular weight of the fatty acid and the saturation of the hydrocarbon chain can be determined by saponification value and iodine-based assay respectively. [20]

c. In-vitro studies:

Lipid digestion models are used for the in vitro evaluation of the lipid-based drug delivery system. The design of an in-vitro testing model is necessary to predict in-vivo performance. This model is also termed as a simulated lypolysis release testing model. The fundamental principle involved in the test remains the system should run at a steady pH during a reaction that consumes or releases the hydrogen ion. If any deviation persists then, it is compensated by the addition of reagents. The model typically consists of temperature-controlled vessels (37°C) in which standard intestinal fluid is composed of bile salt, digestion buffer, and phospholipids. To initiate the digestion lipid-based formulation along with pancreatic along with colipase are added in the model. Once lipid digestion starts liberation of fatty acid and transit drop of pH is observed. The pH electrode coupled with the pH-stat meter controller and auto burette quantifies the drop in pH. An equimolar amount of sodium hydroxide is accurately calculated to titrate the released fatty acids by auto burette to restrict the drop of pH of digestion medium from a preset digestion pH value. Hence, the extent of the digestion can be predicted by the quantification of the rate of sodium hydroxide addition and considering the stoichiometric relationship between sodium hydroxide and fatty acids.

In-vivo studies:

The appropriate in-vivo study is implemented to estimate the impact of excipients on the bioavailability and pharmacokinetics of the drugs. Since the lipid-based formulation increases bioavailability by increasing the intestinal uptake it is very necessary to study the intestinal lymphatic system. Because of the unavailability of sufficient clinical data and variations in the method as well as the animal model used, the study became more complicated. It was reported that the bioavailability of a lipid-based formulation of saquinavir mesylate (Fortovase®) is enhanced up to three folds as compared to Invirase® (saquinavir is a hard gelatin capsule). The mesenteric lymph duct-canulated rat model was performed to identify the mechanism for the improved bioavailability for this formulation. The increased insolubilization and permeability of drugs lead to an increase in the bioavailability of the lipid-based formulation. [21]

Conclusion:

One of the major challenges of lipid excipients and delivery systems is the varying range of compounds they contain. Proper characterization and evaluation of these delivery systems, their stability, classification, and regulatory issues consequently affect the number of these formulations. On the way of conclusion, the prospect of these delivery systems looks promising. Lipid-based formulations may be used to enhance the delivery of a range of drug molecules via oral and parenteral administration. The current theme issue brings together submissions from a range of contributors and has focused largely on lipid-based formulations to enhance the oral absorption of poorly water-soluble drugs, since this continues to be a major impediment to drug development.

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