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A Review on lipid excipient for lipid based drug delivery system

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Abstract

Lipid based drug delivery systems provide an effective way to deliver drugs with different molecular weights (small and large Molecular weight) and bioactive ingredients at specific locations and times. Poorly water-soluble drugs present a challenge to formulation scientists in terms of solubility and bioavailability. Simple oil solutions and complicated blends of oils, co-surfactants, surfactants, and cosolvents are both examples of lipid-based delivery systems. Nevertheless, lipid excipients have the ability to solubilize hydrophobic drugs in the matrix of the dosage form. A decrease in the barriers of poor aqueous solubility and a slow drug dissolution rate in the gastrointestinal (GI) fluids leads to enhanced drug absorption, which is predominantly mediated by these factors. The quantity of potential excipients available to the formulator to select from when creating lipid-based formulations can appear daunting. Several currently available kinds of lipid excipients will be discussed in this review article regarding their pharmaceutically useful properties: Natural oils, fats, fatty acids, and fatty acids Semi-synthetic mono-, di-, and triglycerides, as well as derivatives of glycerides, fatty acids, and cholesterol, as well as Polyglyceryl and phospholipids, as well as Polyglyceryl fatty acid esters.

1. INTRODUCTION

As lipid-based drug delivery systems offer the suitable means of site-specific as well as time-controlled delivery of drugs with different molecular weights, either small or large, and the bioactive agents, significant efforts have been made in recent years to utilize their potentials.¹

Most recently discovered medications exhibit low bioavailability when taken orally because they are hydrophobic. Additionally, because the newly identified chemical entities have high molecular weights and rising lipophilicity, the recent discovered drugs are not suitable for oral administration^{1,2}. As a result, lipophilic drug discovery, formulation, and development are now complicated by the poor aqueous solubility of these drugs. It was clear that up to 70% of recently developed compounds and about 40% of drugs that are currently on the market may have poor water solubility. Due to poor bioavailability and

lack of pharmacological action at the site of action, low water solubility causes insufficient amounts of drugs to enter the systemic circulation.¹ The oral bioavailability is constrained by the poor aqueous solubility and slow dissolution rate. Because of this, creating these therapeutic agents that have the highest oral bioavailability possible is a difficult task. The rate and degree of drug absorption through the GI membrane which is only possible when the maximum percentage of drugs is solubilized in GI contents is another sign of a drug's effectiveness. According to their aqueous solubility and GI membrane permeability, drugs are divided into four classes in the Biopharmaceutics Classification System (BCS). The formulation to increase bioavailability is thought to be challenging for class II drugs (high permeability and low

solubility) and class IV drugs (low permeability and low solubility).³⁻⁵



Fig 1: Rational behind lipid-based drug delivery system

2. GENERAL ROUTES OF LBDDS:

A significant risk factor for developing diabetes is obesity. There are several ways to provide lipid-based drug delivery systems, including oral, parenteral, ophthalmic, intranasal, dermal/transdermal, and vaginal methods (LBDDS). The least costly, least intrusive, and least likely to result in adverse effects, such as responses at the injection site, is the oral route, which is why it is the most often used. It is also seen to be the simplest and most useful method of giving patients long-term therapy. Formulation strategies based on a logical and systematic approach must be devised at an incredibly early stage of development in order to avoid irregular and poor in vitro/in vivo correlations and so boost the odds of formulation development success.⁶

3. LIPID FORMULATION CLASSIFICATION SYSTEM

There A new "type" of formulation was added to the lipid formulation classification system (LFC) in 2006 after it had already been introduced as a working model in 2000. In recent years, the pharmaceutical industry has discussed the LFCs more extensively to reach an agreement that can be used as a framework for comparing the performance of lipid-based formulations.⁶ The main goal of the LFCs is to make it easier to interpret in vivo studies, which will then make it easier to identify the best formulations for drugs

based on their physicochemical properties, which are shown in Table 1.^{6,7}

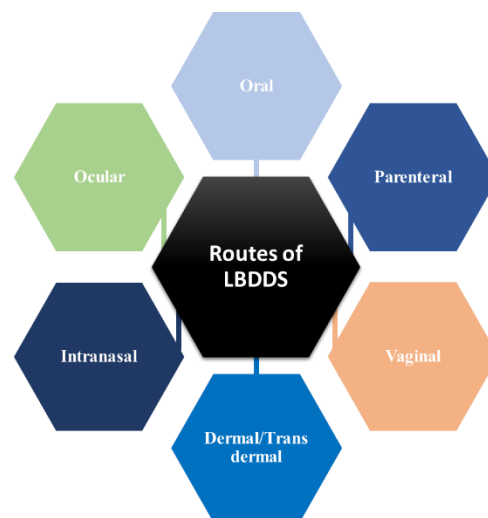


Fig 2: Routes of administration of lipid base drug delivery system.

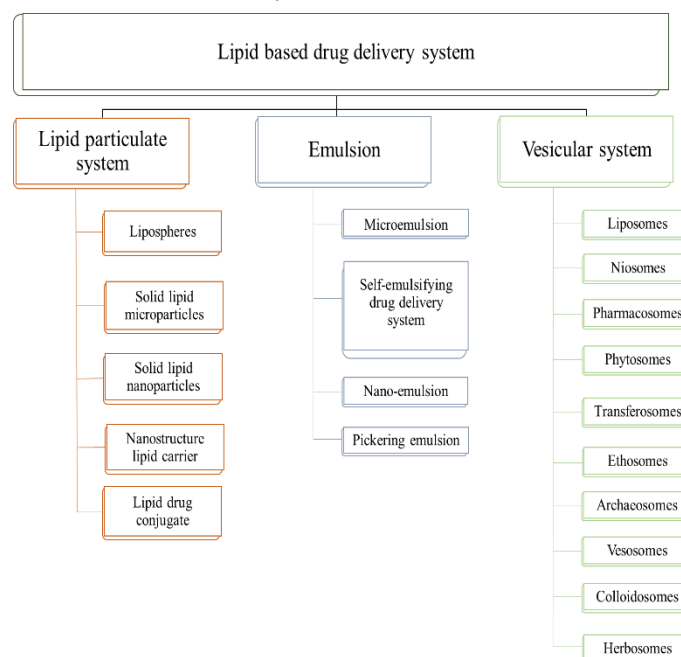


Fig 3: Types of lipid-based drug delivery systems

4. LIPID-BASED EXCIPIENTS FOR ORAL DRUG DELIVERY

An oral lipid-based formulation increases the bioavailability of a weakly water-soluble drug more than an oral solid dose form. Although

Table1.Lipid formulation classification system

Formulation type	Material	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g., tri-, di-, and monoglycerides)	Non-dispersing requires digestion	Generally recognized as safe (GRAS) status; simple; and excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water insoluble surfactants	SEDDS formed without water soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (Particle size 0.25–2 μm)
Type III	Oils, surfactants, and cosolvents (both water-insoluble and water-soluble excipients)	SEDDS/SMEDDS formed with water soluble components	Clear or almost clear dispersion, drug absorption without digestion	Possible loss of solvent capacity on dispersion, less easily digested
Type IV	Water-soluble surfactants and cosolvents	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion may not be digestible

additional methods for improving absorption have also been put up, solubilizing the drug is the primary way that lipid-based formulations enhance bioavailability^{8,9}. These additional methods include slowing down P-glycoprotein-mediated efflux, improving lymphatic transport to mitigate hepatic first pass metabolism, lengthening gastrointestinal (GI) transit time, or guarding against GI tract degradation. The formulator has access to hundreds of possible excipients for lipid-based formulations, and the variety of choices could appear daunting. In order to further confuse customers, it is fairly uncommon for a single excipient to be offered by a number of distinct vendors, each of whom uses a different trade name. Just a limited proportion of lipids have found use in clinical formulation development due to a scant or non-existent history of pharmaceutical application or, more commonly, a lack of regulatory permission. This will review describe the features of the following kinds of lipid excipients that are currently on the market from a pharmacological perspective^{9,10}

- I. Fatty acids, first
- II. Pure fats and oils

- III. Mono-, di-, and triglycerides that are semi-synthetic.
- IV. Semi-synthetic glyceride and fatty acid derivatives in polyethylene glycol (PEG)
- V. Esters of Polyglyceryl fatty acids
- VI. Phospholipids and cholesterol

4.1 FATTY ACIDS

Aliphatic hydrocarbons, whether saturated or unsaturated, can be transformed into monocarboxylic acids, which are fatty acids. The individual fatty acid molecules can be more tightly aligned and interact more favourably because trans fatty acids are more linear in form than their comparable cis counterparts. Because of this, the fatty acids trans form has a greater melting point than its cis counterpart^{10,11}. Naturally occurring cis fatty acids are partly transformed to trans fatty acids during the cleaning up of natural product sources and following hydrogenation procedures. Trans fatty acids are therefore common in the normal western diet. While semi-synthetic PEG fatty acid esters are used as solubilizers, surfactants, and emulsifiers, fatty acids are principally used in pharmaceuticals as solubilizing carriers for drugs that are poorly water-soluble (Table 2). Excipients from either class can be used to create both soft and hard gelatin capsules^{10,12,13}.

Table 2. Fatty Acids

Excipient	Chemical name composition	Trade name	Physical state at 25°C or melting point	Uses
Oleic acid	c-9-Octadecenoic acid	Crodamol EO/Croda Estol ETO3660	Liquid	Vehicle, solubilizer, surfactant
Propylene glycol monolaurate	Monolauric acid ester of propylene glycol	Priolene 6929/Uniqema Crosssential O94	Liquid	Vehicle, solubilizer, co-surfactant in microemulsions
Isopropyl palmitate	Isopropyl ester of palmitic acid	Estol 1517IPP/Uniqema Stepan IPP/Stepan CrosssentialL99	Liquid	Vehicle, solubilizer lubricant, emulsifier
Linoleic acid	c-9, c-12-Octadecadienoic acid	Crosssential L99	Liquid	Vehicle, solubilizer
Propylene glycol monocaprylate	Caprylic acid monoester of propylene glycol	Capryol 90/Gattefosse Capmul PG8	Liquid	Vehicle, solubilizer absorption enhancer co-emulsifier

4.2 NATURAL OILS AND FATS

In naturally occurring oils and fats, triglycerides (TG), which are fatty acid tri-esters of glycerol, are known more accurately (though less commonly) as triacylglycerols. Table 3 includes a list of many well-known natural oils along with their trade names and sources. Triglycerides are naturally

occurring fatty acids with different chain lengths and degrees of unsaturation. Short chain triglycerides (less than five carbons), medium chain triglycerides (between six and twelve carbons), and long chain triglycerides (greater than twelve carbons) are the three groups (more than 12 carbons).¹⁰

Table 3. Lists trade names and suppliers of several common natural oils.

Excipient	Trade name	Physical state at 25°C or melting point
Canola oil	Pureco Canola	Liquid
Coconut oil	Pureco 76 and Coconut Oil EP	Liquid
Corn oil	Super Refined Corn Oil NF and Super Refined Corn Oil NFNP Corn oil	Liquid
Cottonseed oil	Super Refined Cottonseed Oil NF Super Refined Cottonseed Oil NF-NP	Liquid
Palm oil	Palm oil	Liquid
Rapeseed oil	Rapeseed oil and Rapeseed Oil Refined EP	Liquid
Safflower oil	Super Refined Safflower Oil USP and Super Refined Safflower Oil USP-NP	Liquid
Soybean oil	Pureco Soybean and Super Refined Soybean Oil USP	Liquid

4.3 SEMI-SYNTHETIC MONO-, DI-, AND TRIGLYCERIDES

Many commercially available semi-synthetic glycerides provide compositions that are more uniform in addition to naturally occurring

triglycerides (Table 4). These excipients are employed in a variety of controlled release dosage forms and as solubilizing, emulsifying, suspending, and wetting agents. They are compatible with both soft and hard gelatin capsules.^{10,14}

Table 4. Semisynthetic Mono-, Di-, and Triglycerides

Excipient	Chemical name or composition	Trade name	Uses
Glyceryl triacetate (Triacetin)	Triacetic acid esters of glycerol	Captex 500 P and Triacetin	Solubilizer, vehicle
Glyceryl mono-, di-, tribehenate	Mono-, di-, and tri-docosanoic acid esters of glycerol	Compritrol 888	Controlled release, tablet lubricant, and binder
Glyceryl monooleate	Monooleic acid ester of glycerol	Capmul GMO	Emulsifier, solubilizer, wetting agent, vehicle for capsule
Glyceryl tributyrate (Tributyric)	Tributyric acid esters of glycerol	Tributyryn	Solubilizer, vehicle

4.4 SEMI-SYNTHETIC POLYETHYLENE GLYCOL (PEG) DERIVATIVES OF GLYCERIDES AND FATTY ACIDS

These excipients are utilised in self-emulsifying drug delivery systems (SEDDS) and self-micro emulsifying drugs as fluid or thermo-softening semi-solid solubilizing carriers, detergents and wetting agents, and emulsifiers and coemulsifier. delivery systems (SEDDS) (SMEDDS). These

excipients range in HLB value from extremely lipophilic (PEG-6 glyceryl oleate, HLB 3-4) to water soluble, and they can be used with both soft and firm gelatin capsules (PEG-40 hydrogenated castor oil, HLB 14-16). Excipients that are mixes of mono-, di-, and triglycerides with fatty acid esters of PEG are included in Table 5 along with their brand names, suppliers, significant physical features, and typical pharmaceutical applications.^{10,15}

Table 5. Lists several excipients that are mixtures of mono-, di-, and triglycerides with fatty acid esters of PEG.

Excipient	Chemical name composition	Trade name	Uses
PEG-4 glyceryl caprylate/caprinate	Caprylic acid (C8:0) and capric acid (C10:0) esters of glycerol and PEG 200	Labrafac Hydro WL 1219	Vehicle, surfactant, solubilizer
PEG-6 glyceryl caprylate/caprinate	Caprylic acid (C8:0) and capric acid (C10:0) esters of glycerol and PEG 300	Softigen 767 and Sasol Acconon CC-6	Vehicle, water soluble surfactant, solubilizer, coemulsifier
PEG-6 glyceryl linoleate	Mono-, di-, and trilinoleic acid (C18:2) esters of glycerol and mono and diesters of PEG 300	Labrafil M 2125 CS	Vehicle, solubilizer, vehicle for softgels,
PEG-35 castor oil (PEG-35 castor oil castor oil, USP/NF)	Mixture of glyceryl PEG ricinoleate (35 moles of ethylene oxide per mole of castor oil) with fatty acid esters of PEG, free PEGs and ethoxylated glycerol.	Cremophor EL/BASF Etocas 35 NF	Water soluble nonionic, surfactant, vehicle, solubilizer, emulsifier coemulsifier, lipid phase or cosurfactant in microemulsions.

4.5 POLYGLYCERYL FATTY ACID ESTERS

Polyglyceryl fatty acid esters are made up of a sequence of glycerol molecules linked together by ether bonds. After that, the esters are esterified

with one or more fatty acid molecules. various example of Polyglyceryl fatty acid are given in table,(Table 6). Polyglyceryl-6 dioleate is formed when a chain of six glycerol molecules is esterified with two molecules of oleic acid.¹⁰

Table 6. Polyglyceryl fatty acid

Excipient	Chemical name or composition	Trade name	Physical state at 25°C or melting point	Uses
Polyglyceryl-3 oleate	Monooleic acid ester of a 3-glycerol solubilizer, unit chain	Caprol 3GO	Liquid	Surfactant, solubilizer, vehicle, emulsifier
Polyglyceryl-3 dioleate	Dioleic acid [18:1 (9)] ester of a 3 glycerol unit chain	Plurol Oleique CC497	Liquid	Surfactant, solubilizer, vehicle, emulsifier, vehicle for capsules Surfactant, solubilizer, emulsifier
Polyglyceryl-3 stearate	Monostearic acid (18:0) ester of a 3 glycerol unit chain	Caprol 3GS	Liquid	Surfactant, solubilizer, emulsifier
Polyglyceryl-6 dioleate	Dioleic acid [18:1 (9)] ester of a 6 glycerol unit chain	Caprol MPGO and Plurol Oleique	Liquid	Surfactant, solubilizer, vehicle, emulsifier, lubricant, crystallization inhibitor

4.6 CHOLESTEROL AND THE PHOSPHOLIPIDS

Phospholipids and cholesterol are used as solubilizers, detergents, and emulsifiers in mixed micelles and emulsions (Table 7). Furthermore, phospholipids have been used as triglyceride antioxidants and are the primary component of liposomes, which have limited use in the delivery

of oral medicines due to their instability in the GI system. In vitro testing, however, showed that liposomes having a 7:2 molar ratio of cholesterol to distearoylphosphatidylcholine were resistant to pancreatic lipase and bile salts, suggesting that these formulations could be used in oral drug administration.¹⁶

Table 7. Polyglyceryl fatty acid

Excipient	Chemical name or composition	Trade name	Uses
Cholesterol	Cholest-5-en-3_ol	Avanti Polar Lipids	Neutral
Sodium cholesteryl sulfate	Cholest-5-en-3_ol	Sigma-Aldrich	Negative
Phosphatidic acid	Mixture of fatty acid diesters of glycerophosphoric acid	Avanti Polar Lipids	Negative
Dioleoylphosphatidic acid	1,2-Dioleoyl-snglycero-3-phosphate (DOPA)	Avanti Polar Lipids	Negative
Phosphatidylserine	A mixture of 1,2diacyl-sn glycerol- 3-phospho-Lserines with the composition varying with the source.	Avanti Polar Lipids Alcolec PS 90P/ American Lecithin	Zwitterion
Dioleoylphosphatidylserine	1,2-Dioleoyl-snglycero-3- phospho-L-serine (DOPS)	Avanti Polar Lipids	Zwitterion
Hydrogenated egg phosphatidylcholine	A mixture of 1,2hydrogenated diacyl-sn-glycero- 3-phosphocholines from eggs.	Avanti Polar Lipids	Zwitterion

5. LIPID EXCIPIENTS IN PHARMACEUTICAL TECHNOLOGIES

The growing demand for "Novel Drug Delivery Systems" to deal with novel chemical entities that may have weak solubility or permeability, to enhance the delivery of existing drugs, and even to extend product lines is fuelling interest in lipid excipients (generics or super generics).

More intriguingly, natural lipid excipients of "Vegetable Origin" are now playing a larger role in pharmaceutical development in general, and specifically in final pharmaceutical formulations for nearly all routes of administration, including injectable, parenteral IV and IM, as well as oral, topical, rectal, and vaginal. Vegetable oils are derived from seeds, grains, or berries.

Each of these species has its own unique makeup and distribution of fatty structures based on the length of the hydrocarbon chain and the number of unsaturated bonds in the chain. These structural differences influence the physical properties of veggie oils (glycerides). For example, the freezing point of glycerides grows with the length of the hydrocarbon chain but falls with the number of double bonds. Natural vegetable oils are unquestionably important excipients for use in pharmacies, but they frequently fall short of the standards established by the pharmaceutical industry and the drug development process in terms of stability, pharmacopoeia specifications, and, most importantly, the functionality of these excipients in pharmaceutical dosage forms.

For all these reasons, we prefer to focus on "Vegetable Oil Derivatives," lipid-based excipients created through "catalytic hydrogenation" of unsaturated bonds or "esterification or glycolysis" using a range of alcohols such as glycerol, polyglycerol, propylene glycol, or polyethylene glycol. These processes allow us to manufacture "Functional Excipients," which are distinguished mainly by their melting point and HLB value (Hydrophilic Lipophilic Balance). Lipid esters (or fatty acid esters) are created from organic oils by carefully choosing, extracting, purifying, and treating them with alcohol. As a consequence, an ester with exactly specified properties and characteristics is produced.

Because lipid esters are regulated at all phases of production and the finished product is methodically evaluated for purity, physical characteristics, and chemical characteristics, the customer is assured an excipient supply with carefully specified and consistent characteristics.

The most common "Vegetable Oil Derivatives" are polyalcohol esters of digestible fatty acids and various alcohols, partial glycerides, poloxylglycerides (also known as macrogol glycerides by the European Pharmacopoeia), ethoxylated glycerides, and hydrogenated vegetable oils.¹⁰

5.1 Chemical Analysis and characterization of lipid excipients:

A comprehensive collection of analytical techniques is accessible from USP/NF, EP, and the excipient manufacturer.

The precise makeup of lipid excipients in terms of esters, ethers, and fatty acid distribution can be determined using HPLC and GC techniques. Quick assays for excipient characterization, such as,

- Saponification Value linked to the ester function amount, are also accessible as chemical indices.
- Iodine Content as an indicator of hydrocarbon chain concentration.
- The amount of unbound hydroxyl groups is calculated using the Hydroxyl Value.
- Acid Value is a measurement of the quantity of natural (un-esterified) fatty acids.
- Peroxide Value is a metric that is used to measure and monitor oxidative changes.^{8,10}

5.2 Physiological effects of lipid-based excipients

The lipid-based formulation was developed especially for medicines with minimal GI solubility, permeability, and bioavailability. The use of lipid-based excipients is intended to enhance drug pseudo-solubility in Gastrointestinal medium, drug absorption, and bioavailability.¹⁷

5.2.1 In-Vivo pseudo-solubility/micellar solution:

The first goal of an optimum lipid-based formulation is to prevent medication precipitation or interaction with other elements. The ideal lipid-based recipe must provide "Spontaneous

Formation" of an O/W emulsion or a microemulsion (or Nano emulsion) once in touch with the GI medium at 37°C, without the effect of enzymes and bile salt.

5.2.2 Permeability:

A complicated collection of barriers specific to each drug influences permeability. There is significant proof that lipids play a part in the fluidization of intestinal cell membranes, the opening of tight junctions, and the inhibition of efflux processes in most lipid-based surfactants.^{17,18}

5.2.3 Lymphatic absorption:

Lipid networks have been shown to improve medication bioavailability by promoting lymphatic uptake. In general, the lymphatic pathway of absorption offers a fantastic window and chance to enhance the bioavailability of extremely lipophilic drugs with high glycerol solubility and affinity (log P>5).^{18,19}

5.3 Formulation with lipids and lipid derivatives:

The first major use of lipid based excipients is to enhance the bioavailability of weakly soluble medications by boosting solubility or pseudo-solubility, targeting lymphatic transport, and/or

modifying enterocyte-based drug transport and disposition.

Drug sustained release in solid dose forms as a lipidic matrix using direct compression or moist granulation is the second most frequent application, followed by drug coating for flavour concealing (chewable tablet) or drug protection (hydrolyses, oxidation...). Dermal, rectal, or vaginal semisolid dosage forms were also used, where lipid-based excipients enhanced drug diffusion /permeability while keeping good skin/mucosal tolerance.^{8,12,19}

5.3.1 Formulation with lipids and lipid derivatives for oral bioavailability

In general, lipids or lipid derivatives could be used in oral bioavailability pharmaceutical formulations with a single excipient or a combination of several excipients to optimise the final formula, resulting in a variety of systems such as solid dispersions, physical mixtures, liquid/solid solutions, and Self-Micro or Self-Nano Emulsifying Drug Delivery Systems (SMEDDS, SNEDDS), with excipients such as glycerol.^{19,20}

Table 8. Lipid excipient for oral drug delivery

Oral drug delivery	
Lipid excipients for oral drug delivery include solubility and bioavailability enhancers, lubricants, modified release, taste-masking, API protection and suspending agents. Excipients are used in a variety of processes enabling the formulation of different dosage forms, mainly tablets, granules, hard and soft capsules.	
Name of lipid Excipient	Description
Compritol® 888 ATO (GLYCEROL ESTER)	<ul style="list-style-type: none"> • It is the lubricant for challenging pharmaceutical tablets when used at 1 to 3%. • Its inertness eliminates drug excipient incompatibility issues. As mixing time and speed do not affect its efficiency nor tablet hardness, it offers flexibility in formulation development and production. • It is the 'troubleshooting' lubricant for tableting.
Precirol® ATO 5 (GLYCEROL ESTER)	<ul style="list-style-type: none"> • It is ideal for taste masking and API protection when used in a high shear or fluid bed coating process due to the formation of a film coating around the drug particle.
Compritol® 888 ATO (GLYCEROL ESTER)	<ul style="list-style-type: none"> • It is a smart solution to sustain drug release when used at 10 to 25%. It forms an inert matrix from which the drug diffuses slowly over time. Used alone or in combination with HPMC it enables the production of sustained release tablet using a direct compression process and with higher drug load achievable.

A simple "one-excipient" formulation: A simple lipid formulation in which the active component is entirely dissolved in the lipid phase. This mixture is exposed to the action of enzymes and bile salts when consumed orally, resulting in In-Vivo "mixed" micelles; in this instance, the oily phase used must be digestible.

In this instance, the oily phase is linked with other surfactants, enabling emulsification and In-Vivo micelle formation to be independent of biological effects. This formulation is known as SELF (Self Emulsifying Lipid Formulation).

To shield delicate actives from oxidation and hydrolysis, glycerides, and glycerol esters (based on C18-C22 fatty acids) with a high melting point and a low HLB value (1-2) are currently extensively used in hot coating methods without solvent. These coated actives can be taken directly or through direct pressing. These same excipients are also used in tablet lipid matrices, and they are well adapted to all compression methods, including direct compression, dry granulation, and wet granulation with water. Because long-chain lipids are not digested and there is no matrix erosion as in polymeric matrices, the process of active

ingredient release from these lipid matrices is entirely regulated by diffusion (Fick's law). As a consequence, the In-Vitro-In-Vivo correlation is outstanding. Table 8 contains samples and explanations of lipid excipients used in oral medication administration.¹⁹⁻²¹

5.3.2 Formulation with lipids and lipid derivatives for dermal application

Lipid excipients offer numerous advantages to dermal tissues on multiple levels. PEG esters as an emulsifier give a simpler manufacturing method when compared to the conventional procedure (the One Pot Process). Solubilizers such as liquid esters, glycerol esters, polyglycerol esters, and propylene glycol esters offer a wide variety of

solubilizers while also increasing active component skin penetration. The majority of skin actives are chemically compatible. Esters are skin-friendly and have no detrimental adverse effects. Table 9 provides instances and explanations of lipid excipients used in topical medication administration.²²⁻²⁴

Table 9. Lipid excipient for Topical drug delivery.

Topical drug delivery	
Solubilizers, emulsifiers, and viscosity modifying agents are lipid excipients used in topical drug delivery. Emulsifiers provide excellent textural and sensory characteristics. Viscosity agents stabilize formulations while solubilizers improve skin penetration. Excipients are used in creams, emulgels, lotions, foams, microemulsions and gels.	
Name of lipid Excipient	Description
Tefosev® 63	<ul style="list-style-type: none"> It is a multi-functional emulsifier, enabling one-pot process and offering excellent mucosal and skin tolerance. It is used worldwide with a broad range of APIs, including the 'azole' antifungals to treat vaginal infections and mycosis. In combination with Labrafil® M 1944 CS, it delivers exceptional heat stability to topical emulsions
Other emulsifiers like Gelot 64, Apifil, Sedefos75	<ul style="list-style-type: none"> It's in combination with Plurol® Oleique CC 497, Lauroglycol™90 or Capryol®90 offer interesting synergies for transdermal drug delivery.

5.3.3 Formulation with lipids and lipid derivatives for rectal and vaginal applications

For a long time, cocoa butter was the only excipient used as a natural lipid in injections. Many factors

have contributed to the preference for Hard Fat (glycerol esters) over the last 70 years, including the variability of its composition,

Table 10. Lipid excipient for Rectal and vaginal drug delivery

Rectal and vaginal drug delivery	
Lipid excipients for suppository and pessary formulation include hard fat and hard fat with additives. These bases provide excellent physico-chemical stability and optimize drug delivery for a wide range of active pharmaceutical ingredients and manufacturing equipment.	
Name of lipid Excipient	Description
Suppocire® N and M types	<ul style="list-style-type: none"> • These are versatile suppository bases used with numerous APIs, including
(GLYCEROL ESTER)	<ul style="list-style-type: none"> • paracetamol, guaranteeing excellent drug release properties for a fast-acting antipyretic effect.
Ovucire® family (GLYCEROL ESTER& ETHOXYLATED FATTY ALCOHOLS)	<ul style="list-style-type: none"> • It is a hard-fat pessary base delivering enhanced spread ability within the vaginal cavity and good mechanical resistance. As it is non-irritant and provides excellent mucosal tolerance, it is widely used in antifungal treatments.

The instability during storage, the polymorphism phenomenon, chemical incompatibility, tricky manipulation in industry, and commercial availability, which was subject to economic fluctuations. The Hard Fat is well positioned to be an excellent excipient for suppositories and ovule formation, as well as to ease any problems that may emerge with other excipients^{24,25}. Table 10 contains samples and explanations of lipid excipients used in rectal and vaginal drug administration.

6. LIPIDIC EXCIPIENTS IN DRUG DELIVERY FOR SOLUBILITY AND BIOAVAILABILITY ENHANCEMENT

Recent breakthroughs in drug finding and development have led in the creation of highly powerful but weakly water-soluble medications with limited systemic exposure. Drug intake requires drug breakdown in the gastrointestinal system. Prodrug creation, salt formation, and the use of metastable polymorphic forms, co-crystals, and particle size reduction, amorphization of the drug, and the use of natural or synthesised lipids are all used to increase bioavailability. Since the effective commercialization of Cyclosporine lipidic products as Sandimmune in 1981, followed by its reformulation as Neoral, the lipid-based drug delivery method has gotten a lot of focus over the

last two decades. Sandimmune created a polydisperse oil-in-water emulsion in GI fluids and showed limited cyclosporine oral bioavailability while keeping effective exposure after oral administration. In comparison, Neoral emulsified in the Gastrointestinal fluids as microemulsions, increasing oral bioavailability while reducing dietary impact. To assist in processing during product creation and increase the oral bioavailability of weakly water-soluble medicines, a varied variety of lipid excipients with flexible utility is available.^{20,24} Lipidic excipients include solubilizers, triglycerides, mixed glycerides, water-soluble surfactants, water insoluble surfactants, emulsifiers, and solubility boosters. They solubilize and retain the drug solubilized in the gastrointestinal tract, shield it from digestive enzymes, enable the creation of a self-emulsifying system, and eventually enhance the oral bioavailability of weakly water-soluble medications. A lipid-based drug delivery device is an efficient way to transport weakly water-soluble drugs with high lipophilicity (logP). Their advantages include dosage reduction, removal of the food impact, decrease in first-pass metabolism by enabling lymphatic route transfer, and improved physical and chemical stability of the drug product. A lipid-based medication delivery system can be as basic as an oil mixture or as complicated as a self-emulsifying system that

autonomously emulsifies in the presence of an aqueous environment.

These systems can be turned into basic liquid solutions for oral administration or soft or firm gelatin pills. In lipid-based drug delivery systems, the overall daily drug dosage varies from less than 0.25 g/mL to higher than 2000 mg, and the drug dose per capsule ranges from 0.25 g to 500 mg, and for oral solutions from 1 g/mL to 100 mg/mL. A single capsule and oral solution dosage of lipid excipient varies from 0.5 to 5 gm and 0.1 mL to 20 mL, respectively.^{19,20,24,26}

6.1 Role of lipid-based excipients in drug delivery

Because of the availability of lipid excipients with adequate safety profiles and regulatory approval, lipid can be helpful as a carrier for weakly water-soluble medicines. Lipid excipients include long- or medium-chain triglycerides, mixed mono- and diglyceride and polar oils, cosolvents, water-insoluble detergents, and water-soluble surfactants. Oil, surfactant, and co-solvent can be combined to make a lipid-based drug delivery system, which can then be converted to a solid intermediate and given orally in solid dosage form. The lipid composition of food influences lipophilic medication intake, resulting in greater absorption and thus improved bioavailability. Lipidic contents inhibit presystemic metabolism and efflux activity, improve solubility and permeability through gastrointestinal tract walls, and extend GI residence time and lymphatic transfer via various mechanisms. The inclusion of lipid excipients in the formulation can enhance the drug candidate's solubility and dissolution profile, enabling it to be absorbed in a more solubilized state and lowering the impacts of food dependent bioavailability. After ingestion of up to 100 gm per day, dietary lipids and lipophilic nutrients are well taken, and it is known that lipids in food can assist in the uptake of medicines with poor water solubility. As a consequence of combining a weakly water-soluble drug with lipids in a lipid-based drug delivery system, drug solubilization and absorption are enhanced. However, food consumption varies due to factors such as health, age, leisure, and society.

While co-administration of a weakly water-soluble medication with formulated lipids can reduce the variability associated with food as a lipid supply. Because of the lipid itself, as well as by activating physiological processes that result in greater bile salt and phospholipid secretion, lipids can enhance solubilization capacity. Long-chain lipids are helpful for drug solubilization even at low quantities, whereas medium-chain lipids are most effective at high concentrations. Lipidic excipients (primarily surfactants) can suppress gut efflux transporter to enhance drug uptake via a variety of mechanisms, including changes in membrane fluidity, efflux transporter expression variations, and direct interaction with the transporter. By postponing gastric transit time, lipid excipients can expand the time available for dissolution and thus uptake of weakly water-soluble medicines.^{20,26,27}

6.2 Formulation development of lipid-based drug delivery system

If the formulation objectives are carefully examined, lipid-based drug delivery methods can be created successfully. Excipients are chosen based on,

- i. freezing point, fatty acid composition, hydrophilic lipophilic balance (HLB) value, solubility, and disposability.
- ii. Excipient solubility, dissolution/dispersion characteristics, durability, and compatibility testing.
- iii. Choosing a suitable formulation technique for the planned dosage type.
- iv. Creating appropriate animal models to forecast the in vivo performance of the chosen formulation; and
- v. optimising the **formulation while keeping** drug loading and breakdown profile in mind. Lipid-based drug delivery systems include oily liquids, blended micelles, self-emulsifying systems, liposomes, and solid lipid nanoparticles.^{10,13,28}

7. SELECTION CRITERIA OF DRUG AND LIPID EXCIPIENT

a) Drug

Drug prospects with poor uptake owing to dissolution or permeation are good candidates for lipid-based drug delivery methods. Drugs from BCS classes II and IV that are poorly water-soluble are ideal prospects for lipid-based drug delivery methods.

Poorly water-soluble medications are frequently referred to as "brick dust" or "greaseballs" in nature. "Brick dust" medicines have poor water solubility due to strong intermolecular interactions within the crystal lattice structure. As a consequence, developing brick dust drug formulation as a lipid-based drug delivery method is difficult. Drugs with a low freezing point and a high lipophilicity are incapable of creating links with water molecules. The lipid-based drug delivery method could be useful for "grease-ball" medicines that have not exhibited adequate bioavailability using traditional formulation approaches.

The drug's solubility and miscibility with an appropriate lipid excipient should be sufficient to integrate the entire amount into the finished dosage form.

BCS classification can be used to evaluate applicants for eligibility. The solubilization technology guide map, as shown in Figure 2, (10) shows which technique is best suitable for a drug or how much drug loading can be used for a drug based on melting point (T_m), logP, and dosage. This guidance map, however, may not always provide an exact indication of bioavailability because it is dependent on solubility rather than permeability. 20,29,30

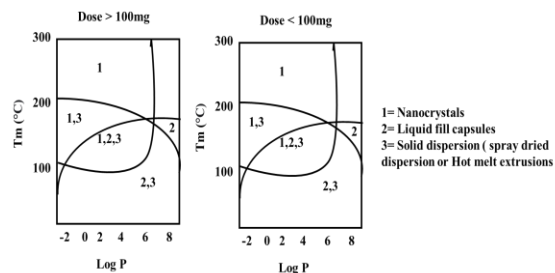


Fig. 4: Solubilization guidance map.

b) Lipid excipient

It is necessary to have a thorough understanding of fatty excipients and their in vivo behaviour, as well as their safety profile and regulatory approval. When selecting a lipid excipient for a lipid-based drug delivery system, miscibility, self-dispersibility and ability to promote self-dispersibility of the formulation, melting point, solvent capacity, fatty acid composition, HLB value, morphology at room temperature, digestibility and fate of digested products, chemical stability, purity, capsule compatibility, and regulatory issues such as irritancy and toxicity are all factors to consider. To effectively create a lipid-based dosage form, it is necessary to observe a favourable dietary influence when the medication is given with a lipid-rich dinner. A comprehensive study of possible incompatibilities between drug and lipid excipient is needed, as is the vulnerability of lipids to oxidation, which can reduce formulation durability. The excipient used in a lipid-based drug delivery system must be generally recognised as safe (GRAS) and lie within the inactive component database limits (IID). Excipients and lipid-based drug delivery methods There are several lipidic excipients available for drug distribution methods, including triglycerides, partial glycerides, semi-synthetic surfactant esters, and semi-synthetic oily esters. The part by Gibson et albook. contains a complete catalogue of lipidic excipients for oral drug delivery. Lipidic excipients with high to low

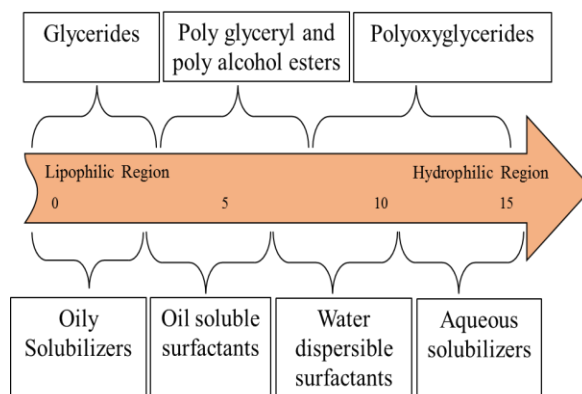


Fig. 5: HLB scale for selection of lipid excipients

HLB are used as a solubility and bioavailability booster, lubricant, drug release modulator, flavour

concealing agent, and drug degradation inhibitor in oral drug administration. Lipid excipients improve drug wettability and solubility, maintain the drug super saturated until it reaches the absorption location in the gastrointestinal system, and allow for selective lymphatic uptake. Drugs that are poorly soluble in water, whether lipophilic or hydrophobic in nature, are more soluble in fatty excipients. The HLB number can be used to calculate an excipient's preference for the watery phase. Generally, lipid excipient or mixture of lipid

excipients with maximal solubilization capability can be selected for creation of formulation.^{31,32}

8. CASE STUDIES OF LIPID-BASED DRUG DELIVERY SYSTEM.

Table 11 displays various lipid-based formulations of lipid base drug delivery systems together with summaries of their lipid excipient, characteristics, and PK (pharmacokinetics) investigations from various research articles.³³⁻³⁷

Table 11. Case studies of lipid-based drug delivery system.

Drug	Properties	Type of formulation	Lipid excipient	Description
Phenytoin	BCS Class II, solubility: 0.032 mg/mL, log P: 2.47, erratic absorption after oral administration, poor aqueous solubility	Emulsion, oily suspension, and aqueous suspension	Corn oil, Polysorbate 80	PK study of corn oil emulsion in adult male albino rats showed. 1.79-folds and 1.29-fold higher AUC in comparison to corn oil suspension and aqueous suspension respectively
Atorvastatin	BCS class II, solubility: 0.02 mg/mL (pH 2.1) and at PH6.0 solubility is 1.23mg/mL, logP: 5.7, pKa: 4.5, High presystolic clearance and first pass metabolism	SMEDDS	Labrafil M19CS, Cremophor RH40, propylene glycol	Pharmacokinetic (PK) study of SMEDDS in beagle dogs showed 1.5 times higher. AUC in comparison to tablet formulation
Simvastatin	BCS class II, solubility: 0.8 µg/mL logP: 4.7, pKa: 14.91	SMEDDS, conventional tablet (Zocor)	Capryol 90, and Carbitol Cremophor EL	PK study was performed in fasted state beagle dogs showed 1.5-fold higher. bioavailability from SMEDDS in comparison to conventional tablet
Itraconazole	BCS II, solubility: less than 10 µg/mL, logP is 6.5, pKa: 3.7	SEDDS and Standard 'Sporanox' formulation	Pluronic L64, Transcutol & tocopherol acetate	PK evaluation in fed state (Lipidic diet) rats showed 3.7-fold increase in AUC of SEEDS in comparison to Sporanox formulation
Danazol	BCS Class II, solubility: 0.0176 mg/mL, logP: 4.6	Long chain (LC) SMEDDS and Medium chain (MC) SMEDDS	Long chain SMEDDS: 30% of soybean oil, 30% of Maisine, Cremophor EL; Medium chain SMEEDS: 36% of MCT, 18% Capmul MCM, Cremophor EL	PK study of LC-SMEDDS was carried out in dogs showed 5-folds greater oral bioavailability in comparison to MC-SMEEDS in fasted state

9. CONCLUSION

Lipids are one of the most adaptable excipient groups available today, providing formulators with an abundance of options for improving and regulating the absorption of poorly water-soluble medicines. The use of lipid-based drug delivery methods can enhance medicine absorption and oral bioavailability of medications that are poorly water soluble. Triglyceride digestion, solubilization, lymphatic absorption, and intestinal permeability are the main processes for increasing the oral bioavailability of weakly water-soluble medications using a lipid-based drug delivery system. A range of lipidic excipients are available for use as solubilizers, surfactants, and wetting agents in lipid-based drug delivery systems, and they can enhance the oral bioavailability of weakly soluble pharmaceuticals by integrating them into different lipid-based drug delivery systems. Lipid-based drug delivery system-based products are also available on the market, suggesting that lipidic excipients have a bright future for lipid-based drug delivery systems.

Consider the following to summarise the importance of these "Vegetable Oil Derivatives" as useful medicinal lipid excipients: The creation of novel excipients (lipidic esters) with appropriate regulation and safety characteristics. Toxin-free or near-toxic conditions. Long-term application modification (drugs intended for chronic diseases). The ability to resist decomposition (especially lipid esters excipients). In terms of medicine durability, high chemical inertness (compatibility). Versatile Material: Available in liquid, solid, atomized particle, and granule shapes. The capacity to adapt to all pharmaceutical kinds, including solid, semi-solid, and liquid. Adaptability to all techniques (pharmaceutical processes). A fluid containing a high concentration of lipidic or hydrophobic active substances (increase solubility). Lipidic excipients may play several functions in increasing sublingual bioavailability. Improving the capillary route to avoid first-pass metabolism. Adapted for drug coating using a heated process with no solvent, for either flavour masking or drug preservation. It has, however, been used as a matrix in continuous release dosage formulations.

10. REFERENCES

1. Kalepu S, Manthina M, Padavala V. Oral lipid-based drug delivery systems – an overview. *Acta Pharm Sin B*. 2013 Dec;3(6):361–72.
2. David J. Hauss -Oral Lipid-Based Formulations. © 2007 by Informa Healthcare USA, Inc. Page no:33-40
3. Chavda H v., Patel CN, Anand IS. Biopharmaceutics classification system. Vol. 1, *Systematic Reviews in Pharmacy*. 2010. p. 62–9.
4. Singhal P, Singhal RV, Kumar VJ, Verma A, Kaushik RD. THE BIOPHARMACEUTICS CLASSIFICATION SYSTEM (BCS): REVIEW *Corresponding Author. 269 Singhal et al *World Journal of Pharmacy and Pharmaceutical Sciences* WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES SJIF Impact Factor 6 [Internet]. 2018;7(1):270. Available from: www.wjpps.com
5. Charalabidis A, Sfouni M, Bergström C, Macheras P. The Biopharmaceutics Classification System (BCS) and the Biopharmaceutics Drug Disposition Classification System (BDDCS): Beyond guidelines. Vol. 566, *International Journal of Pharmaceutics*. Elsevier B.V.; 2019. p. 264–81.
6. Shrestha H, Bala R, Arora S. Lipid-Based Drug Delivery Systems. *J Pharm (Cairo)*. 2014 May 19;2014:1–10.
7. Anand S, Gupta R, Prajapati SK. Self-microemulsifying drug delivery system. Vol. 9, *Asian Journal of Pharmaceutical and Clinical Research*. Innovare Academics Sciences Pvt. Ltd; 2016. p. 33–8.
8. Fundamental N, Beloqui García A, Camilla Bergonzi M, Nakmode D, Bhavana V, Thakor P, et al. Citation: Nakmode, D *Fundamental Aspects of Lipid-Based Excipients in Lipid-Based Product Development*. 2022; Available from: <https://doi.org/10.3390/pharmaceutics14040831>
9. Mu H, Holm R, Müllertz A. Lipid-based formulations for oral administration of poorly water-soluble drugs. Vol. 453, *International Journal of Pharmaceutics*. Elsevier B.V.; 2013. p. 215–24.
10. 2. David J. Hauss -Oral Lipid-Based Formulations. © 2007 by Informa Healthcare USA, Inc. Page no:35-61

11. Associates PB. ENCYCLOPEDIA OF EMULSION TECHNOLOGY VOLUME 3 Basic Theory Measurement Applications Edited by PAUL BECHER.
12. Pouton CW, Porter CJH. Formulation of lipid-based delivery systems for oral administration: Materials, methods and strategies. Vol. 60, Advanced Drug Delivery Reviews. 2008. p. 625–37.
13. Shrestha H, Bala R, Arora S. Lipid-Based Drug Delivery Systems. J Pharm (Cairo). 2014 May 19; 2014:1–10.
14. http://www.sigmaaldrich.com/Area_of_Interest/The_Americas/United_States.html (accessed May 2004). 2004. s
15. The HLB SYSTEM a time-saving guide to emulsifier selection ANTICIPATING NEEDS. 1976.
16. <http://www.abitec.com/> (accessed May 2004). 2004.
17. O'Driscoll CM, Griffin BT. Biopharmaceutical challenges associated with drugs with low aqueous solubility-The potential impact of lipid-based formulations. Vol. 60, Advanced Drug Delivery Reviews. 2008. p. 617–24.
18. Azman M, Sabri AH, Anjani QK, Mustaffa MF, Hamid KA. Intestinal Absorption Study: Challenges and Absorption Enhancement Strategies in Improving Oral Drug Delivery. Vol. 15, Pharmaceuticals. MDPI; 2022.
19. Zhang Z, Lu Y, Qi J, Wu W. An update on oral drug delivery via intestinal lymphatic transport. Vol. 11, Acta Pharmaceutica Sinica B. Chinese Academy of Medical Sciences; 2021. p. 2449–68.
20. Porter CJH, Trevaskis NL, Charman WN. Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs. Vol. 6, Nature Reviews Drug Discovery. 2007. p. 231–48.
21. Nanjwade BK, Patel DJ, Udhani RA, Manvi F v. Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs. Vol. 79, Scientia Pharmaceutica. 2011. p. 705–27.
22. Pavlou P, Siamidi A, Varvaresou A, Vlachou M. Skin care formulations and lipid carriers as skin moisturizing agents. Vol. 8, Cosmetics. MDPI; 2021.
23. Souto EB, Yoshida CMP, Leonardi GR, Cano A, Sanchez-Lopez E, Zielinska A, et al. Lipid-polymeric films: Composition, production and applications in wound healing and skin repair. Vol. 13, Pharmaceuticals. MDPI AG; 2021.
24. Chime A. Lipid-based drug delivery systems (LDDS): Recent advances and applications of lipids in drug delivery. Afr J Pharm Pharmacol. 2013 Dec 29;7(48):3034–59.
25. <https://www.pharmaexcipients.com/oleochemicals/main-functionalities-of-lipid-excipients-for-rectal-vaginal-drug-delivery/>.
26. Kuentz M. Lipid-based formulations for oral delivery of lipophilic drugs. Vol. 9, Drug Discovery Today: Technologies. Elsevier Ltd; 2012.
27. Hauss DJ. Oral lipid-based formulations. Vol. 59, Advanced Drug Delivery Reviews. 2007. p. 667–76.
28. Fundamental N, Beloqui García A, Camilla Bergonzi M, Nakmode D, Bhavana V, Thakor P, et al. Citation: Nakmode, D Fundamental Aspects of Lipid-Based Excipients in Lipid-Based Product Development. 2022; Available from: <https://doi.org/10.3390/pharmaceutics14040831>
29. Chen ML. Lipid excipients and delivery systems for pharmaceutical development: A regulatory perspective. Vol. 60, Advanced Drug Delivery Reviews. 2008. p. 768–77.
30. Rahman MA. For personal use only. 2012.
31. Devi R, Agarwal S. Some Multifunctional Lipid Excipients And Their Pharmaceutical Applications. Int J Pharm Pharm Sci. 2019 Jul 25;1–7.
32. Nanjwade BK, Patel DJ, Udhani RA, Manvi F v. Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs. Vol. 79, Scientia Pharmaceutica. 2011. p. 705–27.
33. H Porter CJ, Marie Kaukonen A, Boyd BJ, Edwards GA, Charman WN. Susceptibility to Lipase-Mediated Digestion Reduces the Oral Bioavailability of Danazol After Administration as a Medium-Chain Lipid-Based Microemulsion Formulation. 2004.
34. Shen H, Zhong M. Preparation and evaluation of self-microemulsifying drug delivery systems (SMEDDS) containing atorvastatin. Journal of Pharmacy and Pharmacology. 2010 Feb 18;58(9):1183–91.
35. Chakrabarti S, Belpaire FM. Bioavailability of phenytoin in lipid containing dosage forms in rats. Journal of Pharmacy and Pharmacology. 1978;30(1):330–1.
36. Kang BK, Lee JS, Chon SK, Jeong SY, Yuk SH, Khang G, et al. Development of self-

microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. *Int J Pharm.* 2004 Apr 15;274(1-2):65-73.

37.Hong JY, Kim JK, Song YK, Park JS, Kim CK. A new self-emulsifying formulation of itraconazole with improved dissolution and oral absorption. *Journal of Controlled Release.* 2006 Jan 10;110(2):332-8.

