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LIPID BASED DRUG DELIVERY SYSTEM: A REVIEW

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ABSTRACT: Poor solubility remains one of the more challenging and critical tasks in drug discovery and development, and it is also the main cause of low bioavailability and poor therapeutic efficacy of the drug. Many solubility enhancement techniques are available in literature like cyclodextrin inclusion complexes, salt formation, solid dispersion, drug delivery carrier approach and prodrug approach are useful, but the most widely used technique for enhancing the solubility of poorly soluble drugs is by encapsulating the drug is lipid-based excipients, which enhances solubilization of the drug in excipient matrix, lead to enhanced bioavailability and improved therapeutic efficacy. Many lipid-based drug delivery systems are available like self-emulsifying drug delivery system (SEDDS), liposomes, solid lipid nanoparticles, nanostructured lipid carrier, which are widely used for lipophilic drugs. In this review, we highlighted some novel mechanisms for drug absorption through lipid-based systems and its commercial applications in the pharmaceutical and biological field.

Keywords: Bioavailability, Lipid excipients, SEDDS, Vitamin E

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INTRODUCTION: About 70% of all new chemical entities (NCE) possess poor aqueous solubility, which causes poor absorption in the GI tract, leads to poor bioavailability. The main causes of poor bioavailability are given in **Fig. 1**. The FDA has divided the new chemical entities into four groups and classified by their aqueous solubility and permeability and give the name as biopharmaceutical classification system [1, 2] **Fig. 2**. The poorly aqueous soluble drugs are also complicated by their variable effect on fed conditions (food effect) which causes more problems in absorption leads to complicated delivery to the targeting area.

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This type of formulations will produce more toxicity, making the formulations more costly and difficult. In the era of modern drug delivery, formulation scientists will realize that the poor oral bioavailability will enhance when co-administered in high-fat meal leads to more interest in lipids as a means of solubilizing the drugs in the GI tract [3, 4].

Lipids are the group of naturally occurring molecules, including fats (triglycerides), waxes (beeswax, aliphatic hydrocarbons), sterols (Cholesterol, phospholipids) and fat-soluble vitamins (Vitamin A, D, E, and K). The biological function of lipids as storing energy in the body and the main structural component of cell membrane [5, 6, 7, 8]. The pharmaceutical importance of lipids in enhancing the absorption of poorly soluble drugs are governed by many mechanisms, including increasing chylomicron production and stimulation of lymphatic transport, alteration (reduction) in gastric transit, preventing drug absorption on intestinal dilution and increasing membrane

permeability. Various lipids are used in drug delivery, including oils (Vitamin E, Captex oil), surfactants (Polysorbate 80, Polyethoxylated 35 castor oil) and all the medium and long-chain triglycerides. Various types of lipid-based drug delivery systems have been used widely like Self emulsifying drug delivery system (SEDDS), solid lipid nanoparticles, microemulsion, nanoemulsion, liposomes and nanostructured lipid carrier for solubilizing the poorly soluble drugs **Fig. 3** this review highlighting the main features of lipid-based drug delivery system and their commercial applications in pharmaceutical industry [9, 10, 11, 12].

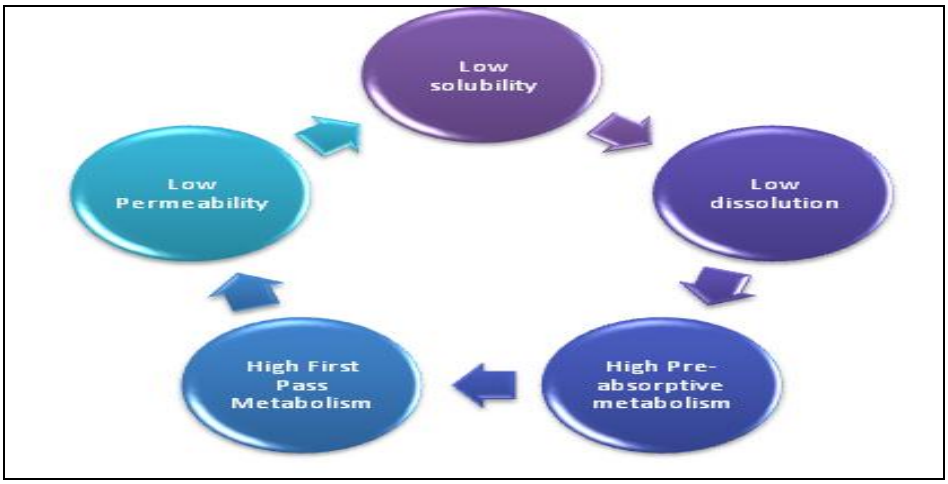

FIG. 1: CAUSES OF POOR ORAL BIOAVAILABILITY

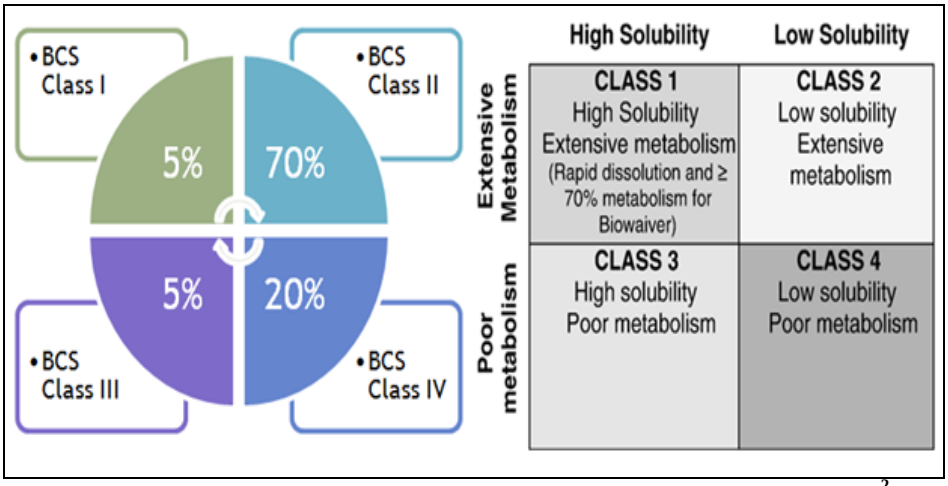

FIG. 2: THE BIOPHARMACEUTICAL CLASSIFICATION SYSTEM [2]

Lipid Formulation Classification System: Lipids are broadly classified into 4 types based upon their particle size, role in drug delivery, composition, characteristic features are their commercial applications. Lipid formulation classification systems play a vital role in selecting the required lipid excipient in selected formulation [13, 14].

TABLE 1: THE MAIN FEATURES OF LIPID BASED CLASSIFICATION SYSTEM ARE GIVEN

LFCS Class	Characteristics	Composition	HLB	Impact of dispersion	Examples
Type I	Pure oils	Oils	N/A	No dispersion	Dutaseride (Avodart)
Type II	SEDDS (Low HLB)	Oils plus surfactant (4:1)	<12	Moderate, forms emulsion (>250nm)	Alfacalcidol (One-Alpha)
Type IIIA	SMEDDS (Intermediate HLB)	Mixture with additional Co-surfactant (20-50%)	>12	Rapid dispersion to form micro-emulsion (100nm)	Ritonavir (Norvir)
Type IIIB	SNEDDS (High HLB)	Mixture with additional Co-solvent (40%)	>12	Rapid dispersion to form nano -emulsion (<100nm)	Cyclosporine (Neoral)
Type-IV	Oil free	Surfactant: Cosurfantant (4:1)	>14	Rapid dispersion to form a micellar solution (<100 nm)	Amprenavir (Agenerase)

Advantages of Lipid Based Drug Delivery Systems: [15, 16]

- Lipid-based formulations solubilize the drug in excipient matrix leads to a substantial increase in drug solubilization as compare to the conventional formulation.
- Eliminates variability associated with reliance on GIT for solubilisation.
- Reduction/elimination of food effect.
- Does not require modification to NCE molecular structure.
- Solvent-free formulation process.
- Pharmaceutical grade excipients and manufacturing equipment readily available.

Role of Lipid-Based Drug Delivery System in Critical Oral Absorption: The oral drug absorption is one of the main factors in designing lipid-based drug delivery systems. The main challenges in critical oral drug absorption are gastric emptying, intestinal transit, dissolution, intestinal based efflux metabolism (cytochrome P450 isoenzymes) and lymphatic transport.

These barriers will limit oral drug absorption in many ways like low solubility, poor dissolution, high first-pass metabolism, and high efflux drug transportation. The lipid-based system is designed to tackle these barriers, which lead to enhance bioavailability and provide the improved systemic drug circulation in the body [17, 18]. The main factors in oral drug absorption and the role of lipids influencing these factors are described in **Fig. 3**.

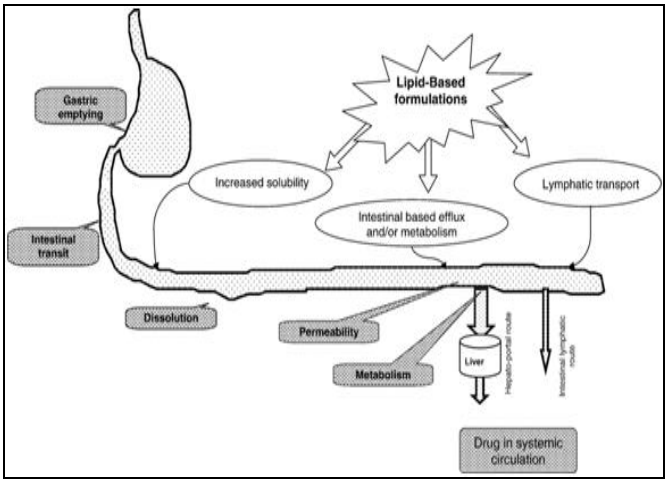

FIG. 3: ROLE OF LIPIDS BASED FORMULATIONS IN CRITICAL ORAL DRUG ABSORPTION

Mechanism of Absorption Enhancement: The lipid formulation in a soft gelatin capsule is first taken orally goes in the stomach where the exogenous lipids convert triglycerides to monoglycerides to free fatty acids by the action of gastric enzyme lipase; this process is known as initial lipid emulsification. The dispersed formulation then goes into the intestine, where pancreatic lipase and co-lipase completes the breakdown of lipids to free fatty acids. These free fatty acids will stimulate the release of bile salts (Phospholipids and cholesterol) in the gallbladder, which combines with lipid digestion products to produce mixed micelles. These mixed micelles contain poorly water-soluble drugs goes into absorption and then into the systemic circulation [19, 20, 21, 22, 23]. Some phospholipids and cholesterol absorb into the surface of emulsion droplets and produces small stable droplets which produce solubilization of lipids. The mixed micelles will provide a lipid environment (lipid solution-emulsion droplet-core of vesicular and micellar phases) which will enhance lymphatic transport of drugs [24, 25, 26, 27, 28].

In general, there are three mechanisms where lipids enhance the absorption of poorly soluble drugs:

- **Increases in Effective Luminal Drug Solubility:** The presence of lipids in the formulation increases the secretion of bile salts and endogenous lipids (Cholesterol, phospholipids) which forms mixed micelles, which leads to solubilizing effect.
- **Alteration (Reduction in Gastric Transit):** Reduction in gastric transit leads to slow delivery to the absorptive site and increasing the time available for dissolution
- **Stimulation of Intestinal Lymphatic Transport:** For highly lipophilic drugs, drugs may enhance the extent of lymphatic transport through inhibition of cytochrome P450 enzymes and P- glycoprotein which is the main transporters for influencing the first pass metabolism [29].

Lipid-Based Systems and Excipients: A wide variety of lipid-based systems have been explored and its broadly classified into three types- emulsion based system, vascular system, and particulate lipid system. These systems have the potential to

solubilize the poorly water-soluble drug in a controlled manner. Each system has its mechanism for solubilization of poorly soluble drugs [31, 32, 33]. The classification of lipid-based drug delivery systems is given in **Fig. 4**.

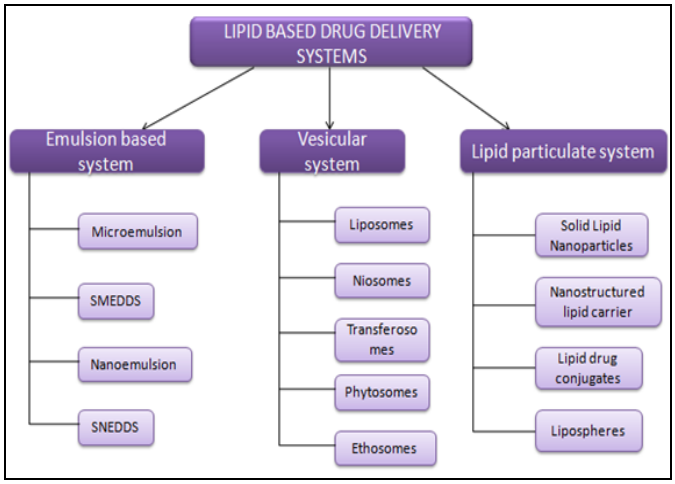

FIG. 4: CLASSIFICATION OF LIPID BASED DRUG DELIVERY SYSTEM

The selection of lipid excipient is a crucial factor in designing the lipid-based drug delivery system. The key formulation factors for lipids and lipophilic excipients are given below:

A) Pharmaceutical Factors: The pharmaceutical factors like solvent capacity, impurity profiling and solid state properties like whether the excipient are solid, semi-solid and liquid are considered for selecting the right excipient in the formulation.

B) *In-vivo* Solubilization Properties: The proper should maintain the drug solubilization on digestion and well as maintain drug solubilization on dispersion.

C) Biochemical Properties: The lipid-based formulations are designed to buy pass the first pass metabolism by inhibiting the cytochrome enzymes and P-glycoprotein, which is the main transporter responsible for metabolism and enhances the lymphatic transport of poorly water-soluble drugs[34].

Lipids are broadly classified into 3 Types:

1. Natural Product Oils: Natural oils or triglycerides containing fatty acids of varying chain length and degree of unsaturation are considered. Examples include castor oil, linseed oil, olive oil.

2. Semi-Synthetics: These excipients having specific physiochemical properties for formulation and are widely used in commercial formulations. Examples include hydrogenated glycerides and macrogol glycerides.

3. Synthetic Lipids: These lipids are considered as surfactants which promote self-emulsification and produces solubilization of drugs through micelles formation. Examples include Vitamin E TPGS, Labrasol *etc*.

TABLE 2: VARIOUS LIPID EXCIPIENTS USED IN COMMERCIAL FORMULATIONS [35, 36]

Water-insoluble excipients	Triglycerides	Surfactants
Bees were oleic acid, soy fatty acids D-α-tocopherol (Vitamin E) corn oil mono-di-glycerides propylene glycol esters of fatty acids medium chain triglycerides	Long chain triglycerides. Hydrogenated soybean oil, corn oil, olive oil, sesame oil, peanut oil. Medium chain triglycerides caprylic triglycerides obtained from coconut oil or palm seed oil	Polysorbate 20, 80 (Tweens) D-α-tocopherol-PEG-1000 succinate (Vitamin E TPGS) polyoxy 35 castor oil (Cremophor EL) PEG 400caprylic /capric glycerides (Labrasols) sorbitan monolaurate (Span20)

TABLE 3: FORMULATION TECHNIQUES FOR LIPID BASED EXCIPIENTS [35, 36]

Formulation techniques for lipid-based formulations	Type of the lipid excipient applied		Formulation limits (%w/w)	
	Liquid	Semi-solid to solid	Maximum lipid Exposure (% w/w)	Maximum drug Loading (% w/w)
Capsule filling	✓	✓	99	50
Spray cooling	✓	✓	99	50
Spray drying	✓	✓	60	50
Adsorption on a solid carrier	✓	✓	80	10
Melt granulation	✓	✓	50	80
Melt extrusion	✓	✓	50	60
Solid lipid nanoparticles	✓	✓	90	50

Formulation Techniques:

Single Component Lipid Solutions: The simplest technique of lipid-based drug delivery comprises of a drug encapsulated in a single lipid excipient. Most commonly used excipient are polyethylene glycols (PEG), or triglycerides. This type of formulation technique depends upon the gastrointestinal capacity to solubilize lipid, and the chances of drug precipitation are high due to its high solubilizing power for poorly soluble drugs. Most commercially based lipid formulations are composed of single component lipid solutions

Self-Emulsifying Formulations: Self-emulsifying drug delivery system (SEDDS) is the thermodynamically stable isotropic mixtures of oil, surfactant, and co-surfactant, that spontaneously forms an emulsion when it's in contact with aqueous fluid in the GI tract. Depending upon the particle size of emulsion droplet, it is classified as SMEDDS (self micro emulsifying drug delivery system) or SNEDDS (Self nanoemulsifying drug delivery system). SMEDDS are a widely used system to solubilize the hydrophobic drugs by partitioning into two phases (oil phase and aqueous phase), which leads to enhance bioavailability. Tacrolimus is a poorly water-soluble drug (1.0 ug/ml), and poor immunosuppressant activity after oral administration, when formulated in SMEDDS will lead to 3 folds higher bioavailability and improved immunosuppressant activity [37, 38].

FIG. 5: CONVERSION OF SMEDDS TO FORMING EMULSION WHEN IT CONTACT WITH AQUEOUS FLUID

Self-emulsifying solid dispersion formulations: These formulations consists of a drug; which is in the finely divided crystalline state, encapsulated in an inert excipient matrix leads to enhance dissolution and subsequent in the GI tract. This type of formulation depends on the micellar co-solvent systems to fully solubilize the drug. These formulations will not be useful commercially due to its poor solubilization capacity and poor stability after storing in extreme conditions

Commercial Applications:

Biotechnology Based Therapeutics: Certain biological based therapeutics like peptides (insulin), vaccines and hormones are chemically known as macromolecules and are ineffective orally due to its degradation by gastric enzymes or its high molecular weight nature.

Lipid-based drug delivery system has the potential to overcome these issues. Testosterone given orally is ineffective in treating androgen deficiency due to its poor oral bioavailability and high systemic first pass metabolism. The lipophilic undecanoate ester has improved oral bioavailability and given orally provide improved androgen activity and less systemic metabolism [40].

Liposomes: Liposomes are lipid-based unilamellar vesicles that are having the capability to encapsulate the drug in the hydrophobic region in the liposomal matrix.

Amphotericin B solubility is just 1.0 µg/ml (Poorly water soluble) have increased the frequency of administration and have severe side effects after oral administration Commercially available liposomal formulation known as fungisome® have bioavailability 3 folds higher (80-85%) and have reduced side effects after oral administration [41, 42].

Self Micro Emulsifying Drug Delivery System (SMEDDS): SMEDDS are the isotropic mixtures of oil, surfactant, and co-surfactant, when exposes to aqueous fluid in the GI tract, it spontaneously forms an emulsion.

Saquinavir is an HIV protease inhibitor is first available commercial in mesylate salt formulation known as Invirase® have poor oral bioavailability (10%), the drug is encapsulated in commercially available lipid-based SMEDDS and formulated in hard gelatin capsule known as forvotrase® have bioavailability 3 folds higher (85%) [43].

TABLE 4: RECENT PATENTS ON LIPID BASED DRUG DELIVERY SYSTEMS

Patent number	Inventor	Publishing date	Abstract
US5906831A	Kare Larsson, Helena Ljusberg-Wahren	06-03-2002	The present invention deals with Controlled release composition of a biologically active material composed of manocaproin that forms reversed micelles structure or a normal micellar structure [44]
WO2003013608A1	Francis Vanderbist, Arthur Deboeck, Philippe Baudier, Antonio Sereno	20-02-2003	The present invention deals with an oral lipid-based pharmaceutical composition containing a PPARα and an HMG-COA reductase inhibitor for the treatment of hypercholesterolemia [45]
US20110039814A1	Hiep Huatan Richard Ross	27-04-2009	The invention relates to pharmaceutical compositions adapted for oral delivery and set the dose frequency according to the circadian rhythm, and including methods for the treatment of hormone-related conditions [46]
US5635536A	Robert T. Lyons	06-03-2007	An acid emulsion comprising a lipid dispersed in an aqueous phase, a cationic sphingolipid, and a required amount of non-ionic surfactant and cholesterol is provided, along with the method of administering the emulsion [47]
US5993858A	John R. Crison Gordon L. Amidon	30-11-1999	The present invention deals with lipid-based formulation for increasing the bioavailability of a poorly soluble drug which includes an oil phase or other lipid material, a surfactant(HLB<12) and a hydrophilic co-surfactant [48]
US6368620B2	Rong Liu, Qinghai Pan, Dennis Lee	09-04-2002	The present invention is related to prepare a formulation comprising a lipid-regulating agent dissolved in a supercritical fluid and then spray it to form the solution through a nozzle to form small particle and forming a suspension of the particles of lipid-regulating agent in a liquid, and collecting the particles [49]
WO2000057859A1	Jitendra P Patel Yeshwant D Sanzgiri John M Lipari Thomas L Reiland	05-10-2000	The present invention is directed to a formulation comprising a lipid-regulating agent dispersed in at least one oil and an emulsifier, the resulting mixture being capable of spontaneously forming an emulsion upon contact with an aqueous medium [50]

TABLE 5: COMMERCIAL FORMULATIONS OF LIPID BASED SYSTEMS [39]

Marketed formulation	Drug name	indication	Dosage form	Company
Neoral®	CyclosporineA/I	Immune Suppressant (T-cell Inhibitor)	Soft gelatin capsule (SGC)	Novartis
Norvir®	Ritonavir	Antiretroviral (protease inhibitor)	Soft gelatin capsule (SGC)	Abbott Laboratories
fortovase®	saquinavir	Antiretroviral (protease inhibitor)	Soft gelatin capsule (SGC)	Hoffman-La Roche Inc.
Agenerase®	Amprenavir	Antiretroviral (protease inhibitor)	Soft gelatin capsule (SGC)	Glaxo smith kline (GSK)
Targetin®	Bexarotene	Antineoplastic (third- generation retinoid)	Soft gelatin capsule (SGC)	Ligand
Rocaltrol®	Calcitriol	Calcium regulator	Soft gelatin capsule (SGC)	Roche
convulex®	Valproic acid	Anticonvulsant and mood-stabilizing drugs	Soft gelatin capsules (SGC)	Pharmacia
Lipirex®	Fenofibrate	Hypolipidaemic drug (Activate lipoprotein lipase)	Hard gelatin capsule (HGC)	Genus
sandimmune®	CyslosporineA/II	Immunosuppressant (T-cell Inhibitor)	Soft gelatin capsule (SGC)	Novartis
Gengraf®	Cyclosporine A/III	Immunosuppressant (T-cell Inhibitor)	Hard gelatin capsule (HGC)	Abbott Laboratories
Accutane®	Isotretinoin	Antiacne (cell differentiation and apoptosis)	Soft gelatin capsule (SGC)	Roche
Avodart®	Dutaseride	benign prostatic hyperplasia (5-α reductase inhibitor)	Soft gelatin capsule (SGC)	Glaxo smith kline(GSK)
Coreg CR	Carvedilol phosphate	Hypertension (β-Blocker)	Hard gelatin capsule (HGC)	Glaxo smith kline(GSK)
Detrol LA	Tolterodine	urinary incontinence (anti muscarinic drug)	Soft gelatin capsule (SGC)	Pharmacia
Aptivus	Tipranavir	HIV Antiviral	Soft gelatin capsule (SGC)	Boehringer Ingelheim
Vesanoid	Tretinoin	Acute promyelocytic leukemia	Soft gelatin capsule (SGC)	Roche

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CONFLICT OF INTEREST: Nil

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