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REVIEW ARTICLE

Lipid Excipients in Self Emulsifying Drug Delivery Systems

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ABSTRACT

It is estimated that 40% of active substances are poorly soluble in water. The improvement of bio-availability of drugs with such properties presents one of the greatest challenges in drug formulations. In recent years, there has been increasing interest in the use of formulations containing lipid based excipients that comprise combinations of synthetic or semisynthetic lipids with surfactants, co-surfactants or co-solvents. The lipid excipients based drug delivery such as Self emulsifying drug delivery system is one of the potential approaches for poorly soluble drugs. Self emulsifying drug delivery system (SEDDS), are isotropic mixtures of oils, surfactants, co-surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. The following article present details on the lipid excipients used in the formulations, their biopharmaceutical aspects, factors affecting their selection for formulation, their role as surfactant, oil or co-surfactant and the various drugs that have been formulated with such type of systems.

Keywords: lipid based excipients, SEDDS, lipophillic

1. INTRODUCTION:

Two-thirds of compounds emerging from the drug discovery channel in recent years have an aqueous solubility <100 µg/mL (0.1 mg/mL) [1]. Owing to their poor aqueous solubility, these drugs lead to poor absorption following oral administration. Such drugs can be categorised into Class 2 and 4 of Biopharmaceutical Classification System (BCS). Problems associated with these drugs include low bioavailability, high intra- and inter-subject variability, increased toxicity and not having dose linearity. A variety of strategies have been adopted for increase in solubility includes use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrin, nanoparticle and solid dispersions. A lipid excipients based drug delivery system, in which the drug is solubilised in lipids or lipid-like excipients, has been recognized as an attractive approach for increasing the bioavailability of these compounds [2, 3]. The primary mechanism by which lipid excipients based formulations enhance bioavailability is through solubilization of the drug, although other mechanisms of absorption enhancement have been implicated and include reduction of P-glycoprotein-mediated efflux, mitigation of hepatic first pass metabolism through enhanced lymphatic transport, alteration in enterocyte based drug transport and disposition [4] prolongation of gastrointestinal transit time, or protection from degradation in the GI tract. They offer a very potential platform for poorly water soluble drugs to get efficiently absorbed in the gastrointestinal tract and give enhanced therapeutic results. Amongst the lipid excipients based formulations the Self emulsifying lipid based formulations provide improvement in rate and extent of absorption of lipophilic compounds resulting in reproducible blood time profiles.

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Primary consideration in self emulsifying formulation is to assess its drug lipophilicity (log P should be more than 4 for lipidipic systems)and solubility in pharmaceutically acceptable lipid based excipients which should be sufficient to allow the entire dose of a drug to be administered in a single dosage unit.[5]

2. SELF EMULSIFYING FORMULATIONS

Self emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants and co-surfactants can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SEDDS can be orally administered in soft or hard gelatin capsules which upon mild agitation (the agitation strength in the human intestine corresponded to 10–30 rpm in the 900 mL- scale paddle method.) [6] followed by dilution in aqueous media such as the gastrointestinal (GI) fluid, these systems can form fine oil in water (o/w) emulsions or micro emulsions [self micro emulsifying drug delivery systems (SMEDDS)]. Potential advantages of these systems include enhanced oral bioavailability enabling reduction in dose, more consistent temporal profiles of drug absorption, selective targeting of drug toward specific absorption window in GIT, and protection of drug from the hostile environment in gut.[7]

3. LIPID EXCIPIENTS

Lipids are molecules made up of the elements carbon, hydrogen and oxygen but in different proportions to carbohydrates. The most common type of lipid is the triglyceride. Lipids can exist as fats, oils and waxes. Fats and oils are very similar in structure (triglycerides). Examples include fat, waxes, certain vitamins, hormones, and most of the non-protein membrane of the cells. They are non-polar in nature, thus soluble in non-polar environments like chloroform but not soluble in water.

Lipid is an essential component of the SEDDS formulations. Not only the lipid can solubilize marked amounts of lipophilic drug or facilitate self-emulsification, but has the propensity to augment the fraction of drug transported via intestinal lymphatic system too, thereby increasing its absorption from the GI tract.[8] Natural edible oils, comprising of medium chain triglycerides, in this regard, are not frequently preferred owing to their poor ability to dissolve large amounts of lipophilic drugs. Modified long and medium chain triglyceride oils, with varying degrees of saturation or hydrolysis, have widely been used for the design and development of SEDDS formulations. These oils offer distinct formulative and physiological advantages, as their degradation products resemble that of the natural end products of intestinal digestion.[2, 4]

4. DESCRIPTION OF LIPIDS

According to Hauss and David [9] presently available marketed classes of lipid excipients presently available are as follows:

- Fatty acids
- Natural oils and fats
- Semi-synthetic mono, di, and triglycerides
- Semi-synthetic polyethylene glycol (PEG) derivatives of glycerides and fatty acids
- Polyglyceryl fatty acid esters
- Cholesterol and phospholipids

Fatty acids

Fatty acids are monocarboxylic acid derivatives of saturated or unsaturated aliphatic hydrocarbons. The fatty acids are not necessarily long chain (C_{14}–C_{20}); they can be medium chain (C_6–C_{12}), short chain (C_4-C_6), unsaturated or branched. Due to these differences in chemical nature, there are numerous lipids or lipid-like excipients available commercially, all of which are colloquially called 'lipids' in the pharmaceutical field for example fatty acids like stearic, oleic, linoleic, and linolenic are all C_{18} carbon compounds. C18 fatty acids and monoglycerides are considerably less polar than their C8 or C12 equivalents and turbid systems that contain larger (~100 nm) vesicular species are evident even at low (>2.5 mM) lipid concentrations.[4]. Medium chain fatty acids are contained in triacylglycerol in general foods. Palm kernel and coconut oils contain about 7% and 14%, respectively, and these are the main sources of medium-chain fatty acids used for foods. Caprylic acid, capric acid are medium chain saturated fatty acids. Amongst the short chain saturated fatty acids acetic acid, butyric acid are the best examples. [10]. Fatty acids find pharmaceutical application primarily as solubilizing vehicles for poorly water-soluble drugs whereas the semi-synthetic PEG fatty acid esters (discussed later) find application not only as solubilizers, but as surfactants and emulsifiers as well.[5]

Natural oils and fats

Naturally occurring oils and fats are comprised of mixtures of various triglycerides (TG) which can be more correctly referred to as triacylglycerols, since chemically they are fatty acid tri-esters of glycerol. Triglycerides are classified as short(<5 carbons), medium (6-12 carbons) and long chains (>12 carbons). Some examples include Rapeseed oil, Safflower oil, Sesame oil, cotton seed oil, soyabean oil etc.

Semi-synthetic mono-, di-, and triglycerides [9]

In addition to the naturally occurring triglycerides, there are several commercially available semi-synthetic glycerides that offer more uniform compositions. These excipients which are compatible with both soft and hard gelatin capsules, find application as solubilizing vehicles,

emulsifiers, suspending, and wetting agents and in various controlled release dosage forms.

Semi-synthetic polyethylene glycol (PEG) derivatives of glycerides and fatty acids

There are several excipients that are mixtures of mono-, di-, and triglycerides with fatty acid esters of PEG, such as Glyceryl distearate (Stepan GDS 386F), Glyceryl tristearate (Imwitor 900), Glyceryl tri-undecanoate (Imwitor 900). The physical aspect, melt characteristics and the HLB of these glycerides vary depending on the nature of the fatty acids present and the degree of esterification with glycerol to yield mono- and diglycerides. [11]

Polyglyceryl fatty acid esters

The polyglyceryl fatty acid esters are composed of a chain of glycerol molecules, linked together by ether linkages, which are esterified with one or more fatty acid molecules. These esters of edible fatty acids are the largest group of vegetable oil derivatives. They are used as solubility enhancers or solubilizers in many lipid based formulations[12]. Some of the examples include PEG-15 hydroxystearate (Solutol –S15), PEG-8 stearate (Mirj 45), polyglyceral oleate (Plurol Oleique CC497).

Cholesterol and the phospholipids

Cholesterol and phospholipids find pharmaceutical application as solubilizers, surfactants, and emulsifiers in mixed micelles and emulsions. Also the phospholipids have been used as antioxidants for triglycerides and are the primary constituents of liposomes, which have found only limited application in oral drug delivery due to instability in the GI tract.[13] Some examples include Sodium cholesteryl sulphate, Phosphatidic acid, Dioleoylphosphatidic acid, Dierucoylphosphatidylcholine.

Lipid excipients	Chemical name	HLB values
Peceol	Glyceryl mono-oleate	3.3
Maisine 35-1	Glyceryl mono-linoleate	4
Imwitor 988	Caprylic/ capric glycerides	3.8
Akoline MCM	Caprylic/capric glycerides	5-6
Compritol 888 ATO	Glyceryl mono-, di-tribehenate	2
Capmul MCM	Glyceryl mono- and dicaprylate/caprate	3-4
Crodamol GTCC	Glyceryl tricaprylate/ caprate	1
Labrafil M 1944 CS	PEG-6 glyceryl oleate	3-4
Labrasol	PEG-8 glyceryl caprylate/ caprate	14
Gleurice 44/14	PEG-32 Glyceryl laureate	14
Cremophor EL	PEG-35 castor oil	12-14
Cremophor RH-40	PEG-40 hydrogenated castor oil	14-16
Plurol oleique CC 497	Polyglyceryl-3 diisostearate	6-7

Table 1: Some common examples of lipid excipients used in self emulsifying formulations with their HLB values and chemical name [5, 14]

Lipid excipients as surfactants and co-surfactants in self emulsifying formulations[14]

Surfactant, is obligatory to provide the essential emulsifying characteristics to the SEDDS. Surfactants, being amphiphilic in nature, can dissolve (or solubilize) relatively high amounts of hydrophobic drug compounds. The surfactants from the natural origin are regarded as much safer than the synthetic ones. The two issues that govern the selection of a surfactant are its HLB and safety. For imparting high self-emulsifying properties to the SEDDS formulation, the surfactant should have a relatively high HLB (i.e., high hydrophilicity) for immediate formation of o/w droplets, and/or rapid spreading of the formulation in the aqueous media. Nonionic surfactants are also considered as safer than the ionic ones.The most widely recommended emulsifiers include the nonionic surfactants with relatively high HLB values like solid or liquid ethoxylated polyglycolyzed glycerides, polyoxyethylene (20) sorbitan monooleate (i.e., Tween 80) and poly(ethylene oxide)-poly(propylene oxide) block copolymers like Pluronic F127. Newer co-surfactants like Transcutol™ and Glycofurol™ have several exceptional advantages over the traditional ones, including better stability and less volatility.

Biopharmaceutical aspects

It is seen that some factors play role because of which the poorly soluble drug becomes more bioavailable due to the presence of some lipids either alone or in combination with food [15]. They are as follows:

1. Alterations in gastric transit time

The lipid and/or food reduce the transit time of the drug and thus, increase the time available for dissolution and there by absorption [16].

2. Increase in effective luminal drug solubility

The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract.[17]

3. Changes in the biochemical barrier function of the GI tract

It is understood that the activity of intestinal efflux transporters may be reduced by the lipids and surfactants this may be indicated by the glycoprotein's efflux pump. Thus lipids and surfactants can reduce the enterocyte-base metabolism. [4]

4. Changes in the physical barrier function of the GI tract

This has been observed that the permeability of drug can be increased by some lipids, lipid metabolism and surfactants. Although, the bioavailability of most of the

poorly soluble drugs do not find problem with passive intestine permeability.[18, 19]

5. Effect of oils on the absorption

Self emulsifying formulations form a fine oil-in-water emulsion with gentile agitation, which may be provided by gastrointestinal motility. A Self emulsifying system also improves the reproducibility of the plasma level-time profile.[20] the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilisation.[21]

Safety issues- irritancy and toxicity
Solvent capacity of the lipid formulation on dispersion which could lead to precipitation of the drug
Digestibility of the excipients and fate of digested products
Morphology at room temperature
Self –dispersibility and role in promoting self –dispersion of the formulation
Chemical stability of lipid excipients
Purity of the lipid excipients and chemical stability
Cost of materials

Table 2. Factors influencing the selection of lipid excipients for poorly water soluble drugs [22, 23, 24,25.26]

Safety issues- irritancy and toxicity

From a regulatory point of view, quality and safety issues related to preclinical and clinical studies are the main difficulties likely to be encountered in launching a lipid-based dosage form on the market, and above all the demonstration of the therapeutic efficacy. The choice of lipid excipients is an important consideration regarding safety of formulation. Water in-soluble surfactants penetrate and fluidize biological membranes and water soluble surfactants have the potential to solubilise membrane components. In general lipid based systems include non-ionic surfactants so it is pertinent to compare the toxicity of non-ionic surfactants. The overall drug stability and absence of immunological reactions to the oils or lipid excipients needs to be demonstrated.

Solvent capacity of the lipid formulation on dispersion which could lead to precipitation of the drug

Use of self emulsifying formulations is limited by their drug loading and limited level of surfactants and co-solvents that can be used with no concern about safety. This may depend on the log P of the drug, and to what extent the surfactant was contributing to its solubilisation within the formulation. In order to predict whether precipitation is likely to occur it is possible to examine the equilibrium solubility of the drug in components of the formulation after maximum dilution, also to carry out corresponding dynamic dispersion/precipitation tests, and then investigate correlations between these two experiments. The formulator must balance the advantage of including co-solvents with the risk of including drug precipitation on dispersion and care is needed while designing these formulations in order to minimize precipitation.

Digestibility of the excipients and fate of digested products

Lipids can roughly be divided into digestible and non-digestible in the gastrointestinal tract. The digestible lipids are composed of dietary lipids such as glycerides, fatty acids, phospholipids, cholesterol and cholesterol esters as well as various synthetic derivatives e.g. triglycerides lipids can be digested and hydrolysed into diglycerides and fatty acids by the lingual and gastric lipases in the stomach. The non-digestible lipids include mineral oil and sucrose polyesters. The digested products are more water soluble than the parent lipids and they can be solubilized within bile salt mixed micelles. On the other hand, the non-digestible lipids when administered they remain in the lumen and can decrease drug absorption by holding a fraction of the co-administered drug.

Morphology at room temperature

One of the challenges faced by lipids is their sensitivity to oxidation, especially for unsaturated triglycerides and fatty acids. It occurs during storage or processing, and leads to a loss in product quality. When lipids are exposed to environmental factors such as light, air or temperature, autoxidation may occur, and can produce change of texture, color, rancid flavor or, generally, loss of quality and even the generation of toxic compounds with health risks for patients. Other degradation pathways are catalyzed by lipoxygenases enzymes. Trace of metals (eg iron, copper, cobalt) can have a significant impact in promoting oxidation. Autoxidation seems to be a key and complex mechanism in lipid oxidation.

Self –dispersibility and role in promoting self –dispersion of the formulation

For the performance of lipid excipients their self dispersion in the formulation are critical parameters. Lipid excipients should promote the self dispersion of the formulation so that the ultimate aim of this delivery system is attained enhancing solubilisation.

Purity of the lipid excipients chemical stability

In relation to the chemical stability of the dissolved drug trace amount of contaminants in lipid excipients is a great issue. Care should be taken to select excipients with low level of peroxides, aldehydes etc., and to find out at an early stage in pre-formulation studies whether the drug used in formulation is sensitive to the particular trace contaminants or not.

Chemical stability of the lipid excipients

Another noticeable consideration relates to the chemical complexity of the lipid excipients. Diversity and versatility of pharmaceutical grade lipid excipients make lipid systems most complex. The use of vegetable oils from different plants is an intermediate source of diversity and subsequent chemical derivation by hydrolysis and esterification adds more to this diversity.

Cost of materials

The lipid excipients whether synthetic or semi-synthetic are costly due to their processing procedure. So, their cost is also an important criteria while selecting them if the formulator desires to make the formulation cost effective.

Drug used	Drug category	Formulation Oil:surfactant:co-surfactant	Ratio of Smix used	Reference
Exemestane	Aromatase inhibitor	Capryol90:CremophorEL: Transcutol HP	3:1	27
Atorvastatin	HMG-CoA reductase inhibitor	Sefsol 218/ Oleic Acid: Tween-20:Carbitol	1:1	28
Valsartan	Angiotensin II receptor antagonist	Castor oil: tween-80:PEG-600	1:1	29
Domperidone	Dopamine antagonists	oleic acid: tween 80: PEG 400	3:1	30
Loratadine	Antihistamine	liquid paraffin/ labrafil: span 20: caproyl PG	3:1	31
Rutin	Vasoprotectant	Edible oil: tween 80 :Capmul MCM-8	1:8	32
Candesartan cilexetil	angiotensin II type 1(AT1) receptor antagonist	Transcutol P : Capryol 90 : Plurol Oleique	2:1	33
Nobiletin	Anti-inflammatory drug	Caprylic-capric triglyceride/tea oil: polyoxyethylene 35 castor oil/polysorbate 80: polyethylene glycol 400	1:1	34
Oleanolic Acid	To treat human liver disease	Sefsol 218: Cremophor EL/Labrasol: Transcutol P	1:1	35
Silymarin	Antihepatotoxic polyphenolic substance	Ethyl oleate/Medium chain triglyceride: Cremophor EL: Transcutol P	2:1	36
Herbal Extract-Garlic Oil Macerate	Antiplatelet action	Herbal extract : Cremophor RH 40: Plurol Oleique	3:1	37
Fenofibrate	Lipid regulating drug	Myritol 318: D-α-tocopheryl polyethylene glycol 1000 succinate: tween 20	4:1	38
Raloxifene	selective estrogen receptor modulator	Capmul MCM C8: Tween-20: PEG-400	3:1	39
Indomethacin	non-steroidal anti-iflammatory	Castor oil : Cremophor RH 40: Capmul MCM-C8	1:8	40
Zedoary turmeric oil	Hepatoprotectant, tumor suppressant, and anti-bacterial agent	ZTO/ethyl oleate: Tween 80: transcutol P	2:1	41

Glyburide	Antidiabetic agent	Capryol 90 : Tween-20 : Transcutol P	1.5:1	42
Cyclosporin A		Labrafil M 1944 CS: Cremophor EL : Transcutol P	2:1	43
Curcumin	anti-tumor, anti-inflammatory, anti-virus, anti-oxidation	ethyl oleate : emulsifier OP/Cremorphor EL: PEG 400	2:1	44
Halofantrine	Antimalarial drug	Soybean oil: Maisine Cremophor EL: Absolute ethanol	3:1	45
Ramipril	Anti-hypertensive drug	Sefsol 218: Tween 80: Carbitol	1:1	46

Table 3: Various drugs and the ratio of Surfactant:Co-Surfactant used in the Self emulsifying formulations

6. CONCLUSION

Lipids can possibly be considered as one of the most versatile excipient classes currently available, providing the formulator with many potential options for enhancing the absorption of poorly water-soluble drugs. The options available may include lipid suspensions, solutions, emulsions, microemulsions, mixed micelles, SEDDS (Self emulsifying drug delivery system), SMEDDS(Self microemulsifying drug delivery system) and liposomes. Though the results with lipid based excipients in Self emulsifying formulations are encouraging but still their use at certain level is limited owing to the factors like stability to oxidation, hydrolysis, and polymorphic changes as well as digestibility and stability in the GI environment that must be considered well enough by the formulator.

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