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ORAL LIPID BASED FORMULATION: A REVIEW

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ABSTRACT

Lipid and surfactant based formulations are exclusively used for poorly aqueous soluble drugs. Lipid based formulations (LBF) include solid, liquid and semi-solid dispersion. These are generally formulated as self emulsifying, non-emulsifying, micro emulsifying drug delivery systems. Lipid excipients are generally obtained from natural sources also can be synthesized chemically. This review summarizes the use of lipid excipients, formulation methods and characterization of lipid based formulations of poorly aqueous soluble drugs. Special attention has been paid to the lipid excipient classes, with special emphasis on their characterization, and various techniques adopted for preparation of liquid, solid and semi- solid lipid formulations.

KEYWORDS

Lipid-based formulations; Oral absorption: Lipid excipients; Formulation techniques.

INTRODUCTION

Recently, it has been estimated that from 40 to as much as 70 percent of all new chemical entities (NCE) entering drug development programs possess insufficient aqueous solubility to allow consistent gastrointestinal absorption of a magnitude sufficient to ensure therapeutic efficacy[1]. The poorly soluble drugs having high permeability, in association with low melting point, critical stability, and low dose (highly potent) are suitable candidate for solid, liquid or semi-solid lipid based formulation which enhances bioavailability of the drug[2, 3]. Depending on the choice of excipient(s) and formulation techniques, it is possible to obtain a variety of systems including physical mixtures, liquid/solid solutions, and Self-Micro or Self-

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Nano Emulsifying Drug Delivery Systems (SMEDDS/SNEDDS)[4,5]. The formulation has to be encapsulated in soft or filled into hard gelatin capsules of which manufacturing process and characteristics of soft capsules have been adequately reported [6- 10].The various methods used for this purpose include melt granulation, adsorption on solid support, spray cooling, spray drying and melt-extrusion/spheronisation[11,12]. These techniques are breakthrough of solid dispersion which involves direct capsules filling and surface active carriers[3]. The lipid excipients are equally important for bioavailability enhancement of poorly aqueous soluble drugs[13,14]. Currently the market value of the lipid formulation comprises an estimated 2–4% of the commercially available drug products surveyed in three markets (UK- 2%, US- 3%, and Japan- 4%) worldwide[15,16].

This review thus begins with definition of the lipid classes, followed by an overview of characterization, and utilization of oral lipid based formulations, and various techniques for the preparation of solid, liquid and semi- solid formulations.

Lipid Based Excipients:

The most frequently chosen excipients for preparing oral lipid-based formulations were dietary oils composed of medium- (e.g., coconut or palm seed oil) or long-chain triglycerides (e.g., corn, olive, peanut, rapeseed, sesame, or soybean oils, including hydrogenated soybean or vegetable oils), lipid soluble solvents (e.g., polyethylene glycol 400, ethanol, propylene glycol, glycerin), and various pharmaceutically acceptable surfactants (e.g., Cremophor® EL, RH40, or RH60; polysorbate 20 or 80; D-α-tocopherol polyethylene glycol 1000 succinate (TPGS®). **Definition and classification of lipid based Excipients:**

Lipids are fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds[17]. They are amphiphilic due to their dual molecular structure i.e. the lipophilic portion consisting of fatty acid(s) and the hydrophilic portion to which the fatty acid(s) are esterified. The melting temperature of lipids commonly increases with the molecular weight (hydrocarbon chain length) and decreases with the unsaturation of the fatty acid and which in turn increases the relative susceptibility to oxidation. Lipids are generally insoluble in water and are often identified by their fatty acid composition, melting point, Hydrophilic-Lipophilic Balance (HLB), and solubility in non-polar organic solvents. Lipids with low HLB and high melting point are suitable for sustained release. Semi-solid excipients and those with high HLB serve as immediate release and bioavailability enhancement excipients[18- 21]. Amongst commonly known lipid classes are fats, oils, waxes, and complex lipids involved in various biological processes such as sterols, phospholipids, glycolipids, lipoproteins and sphingolipids.

Classification of Lipid Excipients:

1. Natural Product Oils

Naturally occurring oils and fats are comprised of mixtures of triglycerides which contain fatty acids of varying chain lengths and degrees of unsaturation. Triglycerides are classified as short (< 5 carbons), medium (6–12 carbons), or long chain (> 12 carbons) and may be synthetically hydrogenated to decrease the degree of unsaturation, thereby conferring resistance to oxidative degradation. Separation of natural product oils into their component glyceride fractions is used to prepare excipients that maximize desirable physical and drug absorption-promoting properties and minimizes susceptibility to oxidation[22, 23.]

2. Semi Synthetic Lipid Excipient

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Several semi-synthetic liquid and thermo-softening (semisolid) excipients, most commonly prepared by chemically combining medium-chain saturated fatty acids or glycerides derived from natural product plant oils, with one or more hydrophilic chemical entities are currently available as pharmaceutical excipients for oral formulation development[24]. These excipients are useful as drug-solubilizing vehicles, surfactants and wetting agents and as emulsifiers and co-emulsifiers in SEDDS and self-microemulsifying drug delivery systems (SMEDDS).

3. Synthetic Lipid Excipients

A number of fully-synthetic, monomeric and polymeric liquid and semi-solid excipients, most of which are glycolic in nature and relatively non-toxic, are used as solvents for formulating poorly water-soluble drugs. These excipients can be used alone or in combination with other lipid excipients to improve the overall solubilizing power of the formulation. Among the polymeric glycol-based excipients finding pharmaceutical application, the polyethylene glycols (PEGs) are a versatile, well-characterized and widely applied class of solubilizers which are available as both liquids and semi-solids. The physical state of these excipients at ambient room temperature is determined by their molecular weights[25]. Propylene glycol, a pharmaceutically-acceptable, monomeric solvent possessing humectants and plasticizing properties, finds application in soft gelatin capsule formulations of poorly water-soluble drugs[26].The poloxamers, which are co-polymers of polyoxyethylene and polyoxypropylene, possess both solvent and surfactant properties and thus find application in the oral delivery of poorly water-soluble drugs [27] . As with the PEGs, they are available in a range of molecular weights which control the physical state of the excipient at room temperature. In addition to improving the bioavailability of poorly water-soluble drugs, they have found application in modified release formulations[28].

4. Surfactants

Various non-ionic surfactants such as the polysorbates (e.g., Tween® 80) and polyoxyls (e.g., Cremophor® EL), which cover the HLB range from 2 to 18, may be used in combination with lipid excipients to promote self-emulsification or microemulsification[29] .Due to their relatively low toxicity, the acceptable quantities for use of these surfactants are limited primarily by their tendency, at high concentrations, to cause brittleness of hard and soft gelatin capsules due to their dehydrating effects on capsule gelatin.

Characterization of Lipid System

1. Chemical Analysis

The exact composition of lipid-based excipients in terms of esters, ethers and fatty acid distribution can be assayed by established HPLC and GC methods. Also, quick tests for excipient characterization are available as chemical indices like: Saponification Value, Iodine Value, Hydroxyl Value, Peroxide Value, Acid Value Analysis for moisture content may also be considered especially for hygroscopic/ high HLB excipients.

2. Physical Analysis

Since lipid based excipients are often processed near or above their melting points, analysis of their thermal behavior at varying stages of formulation is of prime importance. Lipids possess complex chemical compositions that lead to broad melting ranges as opposed to a single melting point. The various physical parameters used for characterization are Differential Scanning Calorimetry (DSC), Nuclear Magnetic Resonance (NMR) hot-stage microscopy (HSM) etc. Nearly all lipid excipients exist under various polymorphs. If on the other hand the formulation matrix is slow or

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incapable of erosion in the dissolution media, polymorphism can significantly affect the drug release properties[30- 34]. However, changes in lipid crystallinity can be controlled by adapted means: tempering at a temperature close to the melting point of the excipient controlling the crystallization rate[32,34] or adding some crystallization seeds to promote the crystallization of one chosen polymorph; or even by adding other excipients such as cellulose ethers, poloxamers or polysorbates to the lipid excipient[35- 37].

3. Dissolution and Dispersion Testing

Lipid-based excipients are subject to digestive processes occurring in the gastro-intestinal tract. Gastric and pancreatic lipases can lipolyze glycerides as well as other esters of fatty acids and alcohols such as PEG esters contained in polyoxylglycerides [38- 40]. Thus digestibility of the excipients should be taken into account during the development of lipid-based formulations[5, 41- 45]. Dispersion testing, i.e. emulsification capacity and analysis of particle size distribution is often used to assess the effectiveness of self-emulsifying formulations. Emulsification capacity is generally evaluated visually[46].

4. Analysis of Physiological Effects of Excipients

Lipid-based excipients can influence oral absorption via various physiological effects such as retarded gastric emptying[47,48] stimulating bile flow and secretion of pancreatic juice[49] increasing the membrane lipid fluidity or acting directly onto enterocytes-based drug transport and disposition[40, 50].

4. Techniques for Solid Lipid Formulation

Techniques for Solid Formulations:

Techniques are chosen on the basis of properties of lipid excipient. The techniques reviewed hereunder facilitate the transformation of liquid or semi-solid formulations into solid particles (powders, granules or pellets) which could subsequently be filled into capsules, sachets or compressed into tablets.

1. Spray Cooling

The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers [51]. Gelucire 50/13 significantly used to enhance drug release profiles for poorly soluble drugs such as diclofenac or praziquantel, but the drug loading capacity is 30% only.[52, 53].

2. Spray Drying

Spray drying is defined as a process by which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction. Polyoxylglycerides (lauroyl or stearoyl) have been used alone or in combination with a solid carrier (silicon dioxide) to form microparticles of etoricoxib and glibenclamide[54,55]. Dry emulsion technology solves the stability problems associated with classic emulsions (phase separation, contamination by microorganism, etc.) during storage and helps also avoid using harmful or toxic organic solvents. Dry emulsions may be redispersed into water before use. Medium chain triglycerides are commonly used as oil phase for these emulsion[56,57]. To promote the bioavailability of a poorly soluble drug amlodipine, oleyl polyoxylglycerides (Labrafil® M 1944 CS) were used as lipophilic phase of the dry emulsion[58].

3. Adsorption on Solid Carriers

Solid carriers are used for the adsorption of liquid formulation to get final solid product and it will be free flowing so that it can be

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compressed or directly filled in hard gelatin capsules. A significant benefit of the adsorption technique is good content uniformity as well as the possibility for high lipid exposure[59]. The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproyl polyoxylglycerides (Labrasol®) formulations that maintained their bioavailability enhancing effect after adsorption on carriers[60- 62].

4. Melt Granulation

Melt granulation or pelletization is a one step-process allowing the transformation of a powder mix containing the drug into granules or spheronized pellets[63, 64]. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder during melt granulation. Nucleation (onset of granule formation) is largely affected by binder viscosity at high impeller speed and binder particle size at low speed[65]. Depending on the combination of process parameters, two distinct mechanisms namely "distribution" and "immersion" may be at play in the development of granules. Fine or atomized excipients with low viscosity at high impeller speed favour a homogenous "distribution" of the binder onto the surface of the powder. Immersion of the powder on the other hand is the preferred mechanism which is assisted by combination of large binder particles possessing high viscosity and mixing under low impeller speed[66, 67]. The granule size distribution is controlled by the combined effect of the impeller and chopper speeds[68, 69]. Generally, lipids with low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB on the other hand may serve in immediate release and bioavailability enhancement[70, 71].

The progressive melting of the binder allows the control of the process and the selection of the granule's size. Also, the melt granulation process may be used for adsorbing semi-solid self-emulsifying systems on solid neutral carriers (mainly silica and magnesium aluminometasilicate)[72,73]. The main advantages of melt granulation/pelletization with lipids are process simplicity (one-step), absence of solvents, and more importantly the potential for the highest drug loading capacity −85% theoretically, and up to 66% actually reported in the literature.

5. Melt Extrusion/ Spheronisaton

Extrusion is a process of converting a raw material with plastic properties into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions[74, 75]. This approach has been successfully tried for 17β-estradiol and two model drugs with surfactants such as sucrose monopalmitate, lauroyl polyoxylglycerides and polysorbate 80 (Tween® 80)[76, 77]. Gelucire® 44/14 to be used directly in the core of the formulation matrix. An innovative "system-in-cylinder" molding technique was recently employed to develop a dual purpose (enhanced bioavailability and controlled release) formulation with propranolol hydrochloride[78, 79, 80]. Melt extrusion is a solvent free process that allows high drug loading as well as content uniformity for low dose high potency actives.

6. Supercritical Fluid Based Method

Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. For environmental reasons, the preferred supercritical fluid of choice is supercritical carbon dioxide. Examples include controlled-release applications using glyceryl trimyristate (Dynasan™ 114) and stearoyl polyoxylglycerides (Gelucire® 50/02)[81, 82]. The technique was successfully applied for

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bioavailability enhancement of carbamazepine using Vitamin E TPGS and Gelucire® 44/14)[83, 84, 85].

7. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers

SLN and NLC are two types of submicron size particles (50– 1000 nm) composed of physiologically tolerated lipid components. SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the glyceryl dibehenate as solid lipid matrix and poloxamers 188 or polysorbates 80 as surfactants. They typically contain a liquid lipid excipient such as medium chain triglycerides in addition to classic components of SLN. They have been mainly used for controlled-release applications in oral[86], intravenous[87] or topical route[88, 89, 90, 91, 92].

Techniques for Liquid and Semi-solid Lipid Formulation:

Capsule filling is the simplest and the most common technology to encapsulate liquid or semi-solid lipid-based formulations. A primary consideration in capsule filling is the compatibility of the excipients with the capsule shell[93, 94]. Prior to filling, in the case of semi-solid or solid lipid-based excipients, the bulk fill reservoir should be heated to maintain the formulation molten and under stirring to avoid phase separation and sedimentation of the drug if dispersed[95].

For filling suspensions into soft capsules, the particle size distribution must be below 250 µm and the viscosity should be controlled to ensure a homogeneous suspension and an easy filling[96. 97]. Numerous publications have described the use of this technology for enhancing drug solubility and absorption via the gastro-intestinal tract. This technique is currently applied in manufacture of various drugs either with soft capsules (amprenavir, calcitriol, cyclosporin, doxercalciferol, isotretinoin, lopinavir, progesterone, ritonavir, saquinavir) or hard capsules (cyclosporin, fenofibrate, ibuprofen, indomethacin, tolterodine) [98, 99, 100]. Only examples of the first three categories are listed below as they are lipid-based or related excipients: (i) 'oils' or lipophilic excipients i.e. medium chain triglycerides corn oil , and acetylated monoglycerides , (ii) 'water-insoluble surfactants': propylene glycol monolaurate glyceryl monolinoleate[101, 102, 103, 104] and (iii) 'water-soluble surfactants': lauroyl polyoxylglycerides , polysorbate, PEG stearate , ethoxylated castor oil ; caprylocaproyl polyoxylglycerides [105].

Characterization:

***In vitro* Characterization**

In vitro means are useful for assessing drug release and provide preliminary guideline for formulation development which depicts *in vivo* evaluation of prototypes; also *in vitro* tests serve to assess batch-to-batch consistency and to ensure that formulation performance is maintained throughout the product shelf-life.

1. Simulated Lipolysis Release Testing:

It is widely recognized that lipid digestibility is an essential determinant of the ability of a lipid to enhance hydrophobic drug absorption. Indigestible lipids, such as paraffin oil, are not only ineffective at promoting drug absorption but have even been reported to inhibit the process, presumably by providing a non-absorbable, lipophilic reservoir from which drug release cannot efficiently occur. in vitro dynamic lipolysis model for studying the effects of simulated lipid digestion on drug solubilization and release from lipid-based formulations[106]. The model has also proven useful in assessing the ability of lipid-based formulations to reduce the positive food effect seen with many poorly water-soluble drugs[107]. The aqueous layer, which

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contains various lipolysis products as well as a diverse mixture of micellar and vesicular entities has been extensively characterized and is of greatest interest in studying the basic mechanisms controlling the GI absorption of hydrophobic drugs[108]. The lipolysis model has proven useful in selecting and optimizing both drug absorption and the resistance to food effect associated with a particular oral lipid-based formulation.

2. *In vitro* Dissolution Testing:

The number of biorelevant dissolution test media and experimental methodologies that have found application in assessing drug release from both lipid-based and conventional oral formulations[109, 110]. Unlike conventional dosage forms, from which the drug substance simply dissolves in the aqueous dissolution test media, lipid-based formulations release the drug from an oily solution which is often immiscible with water.

In vivo Characterization

1. Nonclinical Evaluation

Due to the complex and incompletely understood dynamics of the interaction of these formulations with the gastrointestinal milieu, its testing invariably requires administration of the formulated drug to an animal prior to clinical application, In designing these studies, a number of factors should be borne in mind by the formulator, including animal species, use of anesthesia, dosing volume and route, and the number and types of biological fluid samples to be collected [111, 112].

2. Choice of non-human Test Species

Bile flow in the rat, which lacks a gallbladder, is continuous and substantially more dilute than man or other species which have gallbladders that release bile in response to the presence of food or a sufficient amount of lipid in the GIT By comparison, bile flow in the dog is more similar to that of man and more appropriate model for predicting drug absorption in man, which would reasonably be expected to influence the relevance of these species with regard to projecting drug absorption from lipid based formulations[113, 114].

3. Lymphatic Transport

Intestinal lymphatic system is responsible for a portion of the total uptake of hydrophobic drugs. These drugs are transported to the systemic circulation in association with chylomicrons and very low density lipoproteins (VLDL) [115] and bypass the liver also hepatic first-pass metabolism, which provides a further boost to bioavailability. The process by which lipophilic drugs associate with chylomicrons is balanced by relative drug hydrophobicity (e.g. octanol: water Log P) and solubility in triglyceride[116]. Although lymphatic drug transport remains relatively unexplored, recent investigations are providing some very interesting findings with regard to the mechanistic aspects of chylomicron transport of xenobiotics [117].

CONCLUSION

The most significant issue to consider when formulating poorly water-soluble drugs is the threat of drug precipitation in the lumen of the gastrointestinal tract. The fate of the formulated product can be predicted using a range of *in vitro* tests to investigate the effects of dispersion, digestion, and gastric emptying on the fate of the drug. It would be useful to establish standard test protocols, particularly in the case of the lipolytic digestion test for lipid formulations. The pig model, as an alternative large animal model to accurately predict human data and should be fully validated to include a systematic evaluation of the expression and functional activity of membrane transporters/enzymes in intestinal and hepatic membranes, so that bioavailability data can be better understood and compared from laboratory to laboratory.

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