Oral lipid-based drug delivery systems – an overview

Sandeep Kalepu*, Mohanvarma Manthina, Veerabhadhraswamy Padavala

Department of Pharmaceutical Technology, Shri Vishnu College of Pharmacy, Bhimavaram 534202, Andhra Pradesh, India

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Abstract The formulation of drugs is carried out with the principle objective of enhancing their bioavailability. Poorly water soluble drugs are challenging for the formulation scientists with regard to solubility and bioavailability. Lipid-based drug delivery systems (LBDDS) are one of the emerging technologies designed to address such challenges. Encapsulating or solubilizing the drug in lipid excipients can lead to increased solubilization and absorption, resulting in enhanced bioavailability. Recent advances in these formulation technologies have led to the successful commercialization of lipid-based formulations. This review provides a comprehensive summary and characterization of lipid-based formulations, especially for oral delivery, from both physicochemical and biopharmaceutical perspectives. This review also focuses on the processing techniques necessary to obtain solid lipid-based formulations for oral delivery, along with a brief discussion of lipid excipients and their characterization.

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*Corresponding author. Tel.: +91 9948444546; fax: +91 8816 250863.
E-mail address: sandeepk@svcp.edu.in (Sandeep Kalepu).
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1. Introduction

Drawbacks to intravenous administration, including extravasation of drug or blood, catheter infections, and thrombosis can be prevented by administering the drug orally, making the oral delivery the most popular route of administration. Nonetheless, oral administration is limited by problems related to physicochemical properties of the drug, including poor solubility, low permeability, instability, and rapid metabolism, all of which decrease oral bioavailability.

With the advent of drug design, various molecules have been created that have a potential for therapeutic action. But most of the newly discovered chemical entities are of high molecular weight and belong to biopharmaceutical classification system (BCS) – II, with poor aqueous solubility and high membrane permeability. Hence these two characteristics limit the bioavailability of orally-administered drugs. These drugs have low solubility which leads to low dissolution and limits absorption. This poor solubility not only gives low oral bioavailability but also leads to high inter- and intra-subject variability and lack of dose proportionality. Also, some of these drugs have enhanced bioavailability when co-administered along with food, e.g., halofantrine and danazol. In order to formulate such drugs in a safe and efficacious form, a balance must be maintained between bioavailability, toxicity and disposition within the body. Various techniques like micronization, complexation with cyclodextrins, solid dispersions, permeation enhancers and surfactants have been reported to overcome some solubility and permeability issues.

In the last decade lipids have gained much interest as carriers for the delivery of drugs with poor water solubility. The availability of novel lipid excipients with acceptable regulatory and safety profiles coupled with their ability to enhance oral bioavailability has helped in the development of lipid based formulations as a means for drug delivery. Lipid-based drug delivery (LBDD) systems have gained much importance in the recent years due to their ability to improve the solubility and bioavailability of drugs with poor water solubility. The absorption of drug from lipid based formulation depends on numerous factors, including particle size, degree of emulsification, rate of dispersion and precipitation of drug upon dispersion.

Lipid-based formulations may include oil solution or suspensions, emulsions, self-micro or self-nano emulsifying drug delivery systems (SMEDDS/SNEDDS). Some of the drugs that are successfully marketed as lipid based formulations include efavirenz (Sustiva), saquinavir (Fortovase), ritonavir (Norvir), clofazamine (Lamprene). An appropriate selection of lipid vehicles, formulation strategies and rational delivery system design can lead to the success of lipid based drug delivery systems.

A water-insoluble drug can be formulated as a lipid-based formulation when the drug itself is an oil-like substance (e.g., ethyl icosapentate, tocopherol nicotinate, teopenrene, indomethacin farnesil and dronabinol), or when conventional formulation approaches like granulation or soluble liquids in capsules do not enhance the oral bioavailability. A variety of lipid-based systems composed of simple oil solutions to complex mixtures of oils, co-solvents, surfactants and co-surfactants can be obtained based on the type of excipients and formulation variables. Indeed, these systems can be converted to solid intermediates (powders, granules and pellets) by various techniques and can be filled in hard gelatin capsules or can be compressed into tablets after blending with suitable tableting excipients.

Figure 1 Schematic diagram of mechanisms of intestinal drug transport from lipid-based formulations.

2. Drug absorption

In practice, lipid formulations can be obtained as a result of blending of excipients such as pure triglyceride oils, mixed glycerides, lipophilic surfactants, hydrophilic surfactants and water-soluble co-solvents. These systems increase absorption from the gastrointestinal tract by accelerating the dissolution process, facilitating the formation of solubilized phases by reduction of particle size to the molecular level, yielding a solid-state solution within the carrier, changing drug uptake, efflux and disposition by altering enterocyte-based transport, and enhancing drug transport to the systemic circulation via intestinal lymphatic system.

2.1. Lymphatic system

The lymphatic system plays an important role in the transport of drugs to the systemic circulation, given its extensive drainage network throughout the body. Some of the advantages of lymphatic transport of drug are avoidance of first-pass metabolism and targeting of specific diseases which are known to spread via lymphatics, such as certain lymphomas and HIV. Possible mechanisms by which lipids affect drug absorption, bioavailability and disposition after oral administration are summarized in Fig. 1. The promising mechanisms include facilitating transcellular absorption due to increased membrane fluidity; allowing paracellular transport by opening tight junctions; increased intracellular concentration and residence time by surfactants due to inhibition of P-gp and/or CYP450; IV, lipid stimulation of lipoprotein/chylomicron production.

2.2. Digestion and solubilization

The balance between a drug’s solubility in the aqueous environment of the gastrointestinal lumen and its permeation across the lipophilic membrane of enterocytes determines its rate and extent of absorption. After oral administration of lipid-based
formulations, gastric lipase initiates the digestion of exogenous dietary triglyceride (TG) and formulation TG. Simultaneously, the mechanical mixing (propulsion, grinding and retropulsion) of the stomach facilitates formation of a crude emulsion (comprised of aqueous gastric fluid and lipid digestion products). Later in the small intestine, TG is broken down to diglyceride, monoglyceride and fatty acids by pancreatic lipase together with its cofactor colipase203, acting primarily at the sn-1 and sn-3 positions of TG to produce 2-monoglyceride and free fatty acid23.

Pancreatic phospholipase A2 digests the formulation-derived or biliary-derived phospholipids (PL) by hydrolyzing at the sn-2 position of PL to yield lysophosphatidylcholine and fatty acid24. The presence of exogenous lipids in the small intestine stimulates the secretion of endogenous biliary lipids from the gall bladder, including bile salt (BS), PL and cholesterol. Previously formed monoglycerides, fatty acids, and lysophospholipid (products of lipid digestion) are subsequently incorporated into a series of colloidal structures, including micelles and unilamellar and multilamellar vesicles in the presence of bile salts. The solubilization and absorptive capacity of the small intestine for lipid digestion products and drugs (D) is significantly enhanced due to these formed lipid metabolites. In Fig. 2, the oil droplet in the intestine is represented in different colors to indicate undigested TG in the core (orange) and digested products such as fatty acid (blue) and monoglyceride (green) on the surface of the droplet.

Figure 2 Lipid digestion and drug solubilization process in the small intestine.

2.3. The role of lipids in enhancement of bioavailability

The bioavailability of some of the drugs is increased when co-administered with food1,2. However, many drug molecules have negligible interaction with food. BCS class I drugs are not affected by the presence or absence of food, but class II drugs have an altered absorption when co-administered with food. The reason for such enhanced bioavailability might be attributed to solubility, permeability and inhibition of efflux transporters in the presence of food30. Some of the drugs which show enhanced bioavailability when administered along with food are griseofulvin27, halofantrine6, danazol5, troglitazone and atovaquone20. A guidance document entitled “Food-Effect Bioavailability and Fed Bioequivalence” was issued by FDA in December 2002. The US FDA recommended high fat meals for food-effect studies because such fatty meals (800–1000 cal, 50%–65% fat, 25%–30% carbohydrates and 15%–20% proteins) affect GI physiology and maximize drug transfer into the systemic circulation39.

In particular, it is the lipid component of the food that plays a vital role in the absorption of lipophilic drugs,30 leading to enhanced oral bioavailability. This can be explained by the ability of a high fat meal to stimulate biliary and pancreatic secretions, to decrease metabolism and efflux activity, to increase intestinal wall permeability, and to a prolongation of gastrointestinal tract (GIT) residence time and transport via lymphatic system31. Triglycerides and long chain fatty acids play a major role in prolonging the GIT residence time. Also, a high fat meal elevates the TG-rich lipoproteins which react with drug molecules. This association of lipoproteins with drug molecules enhances intestinal lymphatic transport and leads to changes in drug disposition and finally changes the kinetics of the pharmacological actions of poorly soluble drugs32. This food effect on drug absorption leads to a serious concern about the sub-therapeutic plasma drug concentration when co-administered without food. Such food effect is also a serious problem for drugs with a narrow therapeutic index, where increased bioavailability may lead to serious untoward effects. Hence, control or/and monitoring of food intake is required when dosing such drugs.

However, food-dependent bioavailability can be significantly reduced by formulating the drug as a lipid-based formulation, which can increase the solubility and dissolution of lipophilic drugs and facilitate the formation of solubilized species, from which absorption occurs. Hence, lipid-based formulations can be used to reduce the dose of drug while simultaneously enhancing its oral bioavailability15.

3. Lipid excipients

A wide range of lipid excipients are available from excipient suppliers. Since these lipids affect the absorption process, it is necessary to know the characteristics of various excipients14. The factors that determine the choice of excipients for lipid-based formulations include miscibility; solvent capacity; self-dispersibility and ability to promote self-dispersion of the formulation; digestibility and fate of digested products; regulatory issues – irritancy, toxicity, purity, chemical stability; capsule compatibility; melting point, and cost.

For preparing lipid-based formulations, dietary oils composed of medium and long chain triglycerides, along with various
so solvents and surfactants are frequently chosen. Many lipids are amphiphilic in nature, having a lipophilic portion (fatty acid) and a hydrophilic portion. The melting point increases as the fatty acid chain length increases, but it decreases with the increase in the unsaturation of the fatty acid and also increases the susceptibility to oxidation. A list of solubilizing agents used in lipid-based formulations is mentioned in Table 1.

3.1. Classification of lipid excipients

3.1.1. Triglycerides

The most common excipients used in lipid-based drug delivery are triglyceride vegetable oils. This is one class of lipid which does not present any safety issues, since they are digested and absorbed. Triglycerides can be further classified as long chain triglycerides (LCT), medium chain triglycerides (MCT) and short chain triglycerides (SCCT). The capacity as a solvent for drugs is mainly decided by the effective concentration of ester groups. MCT have a higher solvent capacity than LCT and are less prone to oxidation. Oils from different vegetable sources have different MCT have a higher solvent capacity than LCT and are less prone

Table 1 Solubilizing excipients used in commercially available Lipid-based oral formulations.

<table>
<thead>
<tr>
<th>Water-insoluble excipients</th>
<th>Triglycerides</th>
<th>Surfactants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bees wax, Oleic acid, Soy fatty acids, Δ-α-Tocopherol (vitamin E), Corn oil mono-di-triglycerides, Medium chain (C8/C10) mono and diglycerides, Propylene glycol esters of fatty acids</td>
<td>Long-chain triglycerides</td>
<td>Polysorbate 20 (tween 20), Polysorbate 80 (tween 80), Sorbitanmonolaurate (Span20), Δ-α -Tocopheryl PEG 1000 succinate (TPGS), Glycerylmonoleate, Polyoxyl 35 castor oil (cremophor EL), Polyoxyl 40 hydrogenated castor oil (cremophor RH40), Polyoxyl 60 hydrogenated castor oil (cremophor RH60), PEG 300 oleic glycerides (Labrafil M-1944CS), PEG 300 linoleic glycerides (Labrafil M-2125CS), PEG 400 capryl/capric Glycerides (Labrasol), PEG 1500 lauric glycerides (Gelucire 80/44/14).</td>
</tr>
</tbody>
</table>

Table 2 Composition of fatty acids found in lipid-based excipients.

<table>
<thead>
<tr>
<th>Fatty acid chain length (number of carbons)</th>
<th>Common name</th>
<th>Melting temperature (°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>Caprylic</td>
<td>16.5</td>
</tr>
<tr>
<td>10</td>
<td>Capric</td>
<td>31.6</td>
</tr>
<tr>
<td>12</td>
<td>Lauric</td>
<td>44.8</td>
</tr>
<tr>
<td>14</td>
<td>Myristic</td>
<td>54.4</td>
</tr>
<tr>
<td>16</td>
<td>Palmitic</td>
<td>62.9</td>
</tr>
<tr>
<td>18</td>
<td>Stearic</td>
<td>70.1</td>
</tr>
<tr>
<td>18</td>
<td>Oleic</td>
<td>16.0</td>
</tr>
<tr>
<td>18</td>
<td>Linoleic</td>
<td>–5.0</td>
</tr>
<tr>
<td>18</td>
<td>γ-Linoleic</td>
<td>–11.0</td>
</tr>
<tr>
<td>18</td>
<td>Erucic</td>
<td>6.0</td>
</tr>
<tr>
<td>20</td>
<td>Arachidic</td>
<td>76.1</td>
</tr>
<tr>
<td>22</td>
<td>Behenic</td>
<td>80.0</td>
</tr>
</tbody>
</table>

3.1.2. Mixed glycerides and polar oils

Mixed glycerides are obtained by partial hydrolysis of vegetable oils. The starting material (triglyceride) and the extent of hydrolysis determine the chemical composition of the mixed glycerides produced. Medium chain mixed glycerides are not susceptible to oxidation, have greater solvent capacity and promote emulsification. These polar oily excipients also improve solvent capacity and the dispersibility of the formulation. Sorbitan trioleate (Span 85) is an example of polar oils. Apart from this, oleic acid is also used in a number of commercial products.

3.1.3. Cosolvents

In order to enhance the solubilization process, most marketed drug products use cosolvents. The popular cosolvents used include ethanol, glycerol, propylene glycol and polyethylene glycols (PEG)-400. The reason for their use can be attributed to an increase in the solvent capacity of the formulation for drugs and to aid the dispersion of systems which contain a high proportion of water soluble surfactants. However, there are several practical limits related to these cosolvents, including precipitation of the solubilized drug from the solvent due to loss of the solvent capacity following dilution, immiscibility of some cosolvents with oils, and incompatibilities of low molecular weight solvents with capsule shells.

3.1.4. Water-insoluble surfactants

A group of lipid excipients with intermediate hydrophilic-lipophilic balance (HLB of 8-12) that adsorb at oil-water interfaces are available. Depending on the degree of ethoxylation, these have a finite solubility in water. They can form emulsions if subjected to shear and are sometimes referred as being ‘dispersible’ in water. These substances can form micelles but are unable to self-emulsify due to their insufficiently hydrophilic nature. Oleate esters such as polyoxyethylene (20) sorbitan trioleate (Tween-85) and polyoxyethylene (20) glyceryl trioleate (Tagot-TO) are typical examples of water-insoluble surfactants whose HLB values are between 11 and 11.5. However, a blend of Tween-80 and Span-80 with average HLB value of 11 is not similar to Tween-85 in function. The former consists of both water-soluble and water-insoluble molecules, but the later consists of predominantly of water-insoluble molecules.
3.1.5. Water-soluble surfactants

These are the most commonly used surfactants for the formulation of self-emulsifying drug delivery systems. The materials with HLB value of approximately 12 or greater can form micellar solutions at low concentrations by dissolving in pure water above their critical micellar concentration. These materials can be synthesized by mixing polyethylene glycols (PEG) with hydrolyzed vegetable oils. Alternatively, alcohols can be made to react with ethylenedioxy to produce alkyl ether ethoxylate, which is a commonly used surfactant (e.g., cetostearyl alcohol ethoxylate 'cetomacrogl'). A reaction of sorbitan esters with ethylene oxide produces polysorbates (predominantly ether ethoxylates).

Cremophor RH40 and RH60 (ethoxylated hydrogenated castor oil) are examples of this type which are obtained from hydrogenation of materials derived from vegetable oils. Cremophor EL (ethoxylated castor oil), which is not hydrogenated is also widely used. Cremophor is known to enhance the absorption by inhibiting the efflux pumps, but the mechanism of inhibition is not yet determined. This might be attributed to a non-specific conformational change due to penetration of the surfactant molecules into the membrane, adsorption on to the surface of the efflux pumps, or interaction of molecules with intracellular domains of efflux pump.

3.1.6. Additives

In order to protect the formulation from oxidation, various lipid soluble anti-oxidants such as α-tocopherol, β-carotene, propyl gallate, butylated hydroxytoluene (BHT) or butylated hydroxyanisole (BHA) can be used.

3.2. Characterization of lipid systems

3.2.1. Physical analysis

Analysis of the thermal behavior of lipids during formulation is of primary importance, since lipid excipients have complex chemical compositions that lead to broad melting ranges. Various thermal properties of lipids including crystallization temperature, melting point, glass transition temperature and determination of solid fat content of the excipient versus temperature can be evaluated using differential scanning calorimetry (DSC). The organization of the lipid during heating or cooling can be assessed by hot-stage microscopy. Crystallinity of a lipid excipient can be confirmed by X-ray diffraction (XRD).

3.2.2. Chemical analysis

High performance liquid chromatography (HPLC) and gas chromatography (GC) can be used to determine the exact composition of ethers, esters and fatty acid distribution. Other chemical indices are also available: the molecular weight of fatty acids can be determined from their saponification value; the saturation of hydrocarbon chains can be measured using an iodine-based assay; oxidative changes can be determined by measuring peroxides; free fatty acids can be measured from acid content; and free hydroxyl groups can be determined by measuring hydroxyl group content.

3.2.3. Dissolution in biorelevant media and dispersion testing

The FDA requires conventional USP dissolution testing as a quality control tool for the formulations, but this dissolution does not correlate to the in vivo behavior of lipid-based formulations. In the GIT lipids are subjected to digestion processes in the presence of gastric and pancreatic lipases. These lipases also affect the emulsification and dispersion properties of the lipid excipients, leading to altered solubilization capacity in vivo. Hence, the digestibility of the lipid excipients must be considered when selecting lipid-based formulations. To assess such effects and predict in vivo behavior, dissolution testing in biorelevant media can be helpful. The effectiveness of self-emulsifying formulations can be determined by dispersion testing (emulsification capacity and particle size). Photon correlation spectroscopy (PCS) or laser light diffraction can be used to measure the particle size, and visual observation can be helpful to predict emulsification capacity.

3.2.4. Analysis of physiological effects of excipients

Lipid-based excipients are known to enhance the oral absorption of drugs by affecting various physiological processes. These include stimulating bile flow and pancreatic juice secretion, prolonging gastric emptying, increasing the membrane fluidity, opening of tight junctions, promoting lymphatic transport of drugs, thus avoiding first pass metabolism, and inhibiting efflux transporters. In order to assess these effects various in vitro models are available, including intestinal microsomes, Caco-2 cells, everted gut sac, Using chamber, and in situ perfusion assays.

3.3. Regulatory status of lipid excipients

Not all excipients are inert substances, and some may be toxic at increased concentrations. In the Code of Federal Regulations, the FDA has published a list of substances that are generally recognized as safe (GRAS). Apart from this, it also maintains a list of inactive ingredients for excipients entitled Inactive Ingredient Guide (IIG) that are approved and can be incorporated in marketed products. This guide provides the list of maximum amount allowed for excipients, which can be used for a specific route of administration. Once an inactive ingredient has been approved for a product through a particular route of administration, it can be used in any new drug formulation and does not require extensive review. The formulator can take the information from both GRAS and IIG when developing a new formulation. Currently, the FDA does not have any process or mechanism to evaluate the safety of excipients individually. Instead, the excipients are reviewed and approved as ‘components’ of the drug or biological product in the application. Since excipients play an integral part in the formulation and cannot be reviewed separately from the drug formulation, the regulatory process is appropriate from a scientific standpoint.

4. Lipid-based formulations

4.1. Lipid formulation classification system

A working model of a lipid formulation classification system (LFCS) was introduced in 2000 and an extra type of formulation was added in 2006. The in vivo behavior of the formulation can be interpreted easily by LFCS. With reference to the physicochemical properties of specific drugs, the most suitable formulation can be identified through LFCS. Table 3 shows the various classes of LFCS. Most of the marketed products are Type III systems, which are diverse with a wide range of oil- and water-soluble substances. Hence, this group has been further divided into Type III A (oils) and Type III B (water-soluble) based on the proportion of oils and water-soluble substances.
4.2. Formulation approaches

Lipid-based drug delivery systems can be developed successfully by careful consideration of the formulation objectives. Table 3 indicates the list of commercially available lipid-based products41. The systematic approach includes pre-selection of excipients based on their melting point, fatty acid composition, HLB value, digestibility and disposability; screening of selected excipients for solubility, dissolution/dispersion properties, stability and compatibility; identification of a formulation technique which is suitable for the intended dosage form; design of appropriate animal models to predict the in vivo performance of the chosen formulation; and optimization of the formulation considering the drug loading and dissolution profile.

<table>
<thead>
<tr>
<th>Type I</th>
<th>Type II</th>
<th>Type IIIA (fine emulsion)</th>
<th>Type IIIB (microemulsion)</th>
<th>Type IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oils without surfactants</td>
<td>Oils and water insoluble surfactants</td>
<td>Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)</td>
<td>Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)</td>
<td>Water-soluble surfactants and cosolvents (no oils)</td>
</tr>
<tr>
<td>Non-dispersing</td>
<td>Emulsion (SEDDS)</td>
<td>SEDDS/SMEDDDS formed with water-soluble components</td>
<td>SEDDS/SMEDDDS formed with water-soluble components and low oil content</td>
<td>Disperses typically to form a micellar solution</td>
</tr>
</tbody>
</table>

4.2.1. Oily liquids

Some drugs are highly lipophilic and have solubility in oils only, e.g., steroids, and are solubilized in triacylglycerols only. Such drugs have to be formulated as oily liquids by solubilizing the drug in oil. But the quantity of oil required to dissolve a unit dose of drug is very high, which restricts or limits the usage of drug in oil formulations. An oily solution of bupivacaine free base was formulated, using a mixture of fractionated coconut oil (Viscoleo®) and castor oil by Larsen et al.63. The formulated oily liquid showed a prolonged local analgesic activity and reduced systemic toxicity when administered subcutaneously to male Wistar rats.

4.2.2. Mixed micelles

These systems consist of more than one molecular species. These micelles represent a disc like structure and resemble a lipid bilayer. In detergent-lipid mixed micelles, the detergent molecules shield the lipid molecules against water at the edges. Increased activity against taxol-resistant and sensitive lung cancer cell lines was observed when paclitaxel and parthenolide were co-encapsulated in mixed micelles of PEG 2000–distearoyl phosphatidylethanolamine (DSPE) and Vitamin E TPGS64. Chen et al.65 reported enhanced anti-tumor activity of methotrexate against multidrug resistant tumors when conjugated with polymeric mixed micelles (composed of Pluronic F127 and P105).

4.2.3. Self-emulsifying systems

As the name suggests, these systems have the ability to emulsify due to the presence of one or more surfactants in addition to the oily phase. The lipophilic drug is solubilized in the oily vehicle. The surfactant helps in dispersing the oily vehicle in the GI fluid, which leads to the formation of a micro-emulsion. Depending upon the size of the emulsion particles, these systems can be further classified as self-micro emulsifying drug delivery systems (SMEDDS) or self-nano emulsifying drug delivery systems (SNEDDS). The formulation generally consists of drug, oily vehicle, surfactant, co-surfactant and even co-solvents. Puerarin SMEDDS sustained release pellets for oral delivery were developed using castor oil as the oil phase, Cremophor® EL as the emulsifier, and 1,2-propanediol as the co-emulsifier by Zhang.
et al.\textsuperscript{66}. The formulated self-emulsifying pellets provided a sustained drug release while simultaneously improving the oral bioavailability of puerarin.

4.2.4. **Liposomes**

Liposomes have spherical bilayer structures which resemble the cell membrane in their arrangement. The lipids mainly used are phospholipids, which are amphipathic in nature, having a hydrophilic head and hydrophobic tail (fatty acid). These phospholipids when hydrated in water form spherical bilayer structures, orienting with their hydrophobic part facing each other (toward inside) and hydrophilic part facing outwards. The advantage of these systems is that hydrophilic substances can be embedded in the aqueous internal spaces of the globules, while hydrophobic drugs can be embedded within the inner fatty acid layers. Propylene glycol liposomes loaded with epirubicin have been reported to overcome multi-drug resistance in breast cancer. These liposomes showed a good permeability to both the cell membrane and nuclear membrane of the tumor cell\textsuperscript{67}.

4.2.5. **Solid lipid nanoparticles**

Recently, solid lipid nanoparticles (SLN) have gained much interest due to their ability to enhance bioavailability along with controlled and site-specific drug delivery. Hence they are exploited as probable possibilities as carriers for oral intestinal lymphatic delivery. SLNs are typically spherical particles (size range 10–1000 nm) with a solid lipid core matrix (stabilized by surfactants) that can solubilize lipophilic molecules. Lipids mainly used include monoglycerides (e.g. glycerol monostearate), diglycerides (e.g. glycerol behenate), triglycerides (e.g. tristearin), fatty acids (e.g. stearic acid), steroids (e.g. cholesterol), and waxes (e.g. cetyl palmitate). As reported by Venishetty et al.\textsuperscript{68}, the oral bioavailability of carvedilol could be improved by formulating a polymer (N-carboxymethyl chitosan) that coated carvedilol solid lipid nanoparticles. Monoglyceride was used as the lipid along with soya lecithin and poloxamer 188 as surfactants for the formulation of carvedilol-loaded SLN.

4.3. **Conversion of liquid–lipid formulations to solid intermediates**

Oral delivery is the most preferred and popular route of drug administration. Liquids and solids can be given through oral route. With regard to the physical and chemical stability of liquids and semisolids, these can be transformed into solid particles (powders or granules), which can be filled into capsules or alternatively compressed into tablets by selecting suitable tableting excipients.

4.3.1. **Spray congealing**

This is also referred to as spray cooling. In this method, molten lipid is sprayed into a cooling chamber and, on contact with the cool air, congeals into spherical solid particles. The solid particles are collected from the bottom of the chamber, which can be filled into hard gelatin capsules or compressed into tablets. Ultrasonic atomizers are frequently used to generate solid particles in this spray cooling process. The parameters to be considered are the melting point of the excipient, the viscosity of the formulation and the cooling air temperature inside the chamber to allow instant solidification of the droplets. Praziquantel granules were prepared by melt granulation using PEG 4000 or Poloxamer 188 as a meltable binder and lactose monohydrate as filler\textsuperscript{69}. In another study by Cavallari et al.\textsuperscript{70}, microparticles with narrow size distribution were obtained when stearoyl polyoxyglycerides (Gelucire\textsuperscript{8} 50/13) were used as an excipient and significantly enhanced the drug release of poorly water soluble drugs like diclofenac.

4.3.2. **Spray drying**

This method is somewhat similar to previous one, but differs in the temperature of the air inside the atomizing chamber. In this method, the drug solution (drug in organic solution/water) is sprayed into a hot air chamber, where the organic solvent or water evaporates giving rise to solid microparticles of drug. During this process, along with the lipid excipients, solid carriers like silicon dioxide can be used. Gelucire\textsuperscript{8} (lipid excipient), enhances the drug release process by forming hydrogen bonds with the active substance, leading to the formation of stable solids of amorphous drug in microparticles\textsuperscript{71,72}. Solid dispersions of glibenclamide were prepared using a spray drying technique by Chauhan et al.\textsuperscript{72}. In this method, glibenclamide was dissolved in sufficient solvent to yield a clear solution. Silicon dioxide was added and the resulting suspension was spray-dried using a spray dryer under fixed conditions of inlet and outlet temperature, feed rate and atomization air pressure.

4.3.3. **Adsorption onto solid carrier**

This is a simple process onto solid carrier and economical (in the context of equipment investment). In this method, a liquid–lipid formulation is adsorbed onto solid carrier like silicon dioxide, calcium silicate or magnesium aluminometasilicate. The liquid–lipid formulation is added to the carrier by mixing in a blender. The carrier must be selected such that it must have greater ability to adsorb the liquid formulation and must have good flow property after adsorption. Gentamicin and erythropoetin with caprylocapryol polyoxyglycerides (Labrasol\textsuperscript{8}) formulations were successfully converted into solid intermediates whose bioavailability was maintained even after adsorption on carriers. Advantages of this method include good content uniformity and high lipid exposure\textsuperscript{73–75}. Ito and co-workers have developed a solid formulation of gentamicin using emulsifier and adsorbent. Using solid adsorbents like calcium silicate, magnesium aluminometasilicate and silicon dioxide, the liquid mixture (drug and emulsifier like Labrasol\textsuperscript{8}) was converted to a solid by a kneading process.

4.3.4. **Melt granulation**

This is also referred as pelletization, which transforms a powder mix (with drug) into granules or pellets\textsuperscript{76–78}. In this method a meltable binder (molten state) is sprayed onto the powder mix in presence of high-shear mixing. This process can be referred to as a ‘pump on’ technique. Alternatively, the meltable binder is blended with powder mix and due to the friction of particles (solid/semisolid) during the high-shear mixing, the binder melts. The melted binder forms liquid bridges between powder particles and forms small granules which transform into spheroidized pellets under controlled conditions. Depending on the fineness of the powder, 15%–25% of the lipid-based binder can be used. The parameters to be considered during the process are binder particle size, mixing time, impeller speed and viscosity of the binder on melting\textsuperscript{79}. The dissolution rate of diazepam was improved by formulating melt agglomerates containing solid dispersions of diazepam by Seo et al.\textsuperscript{80}. Lactose monohydrate was melt-agglomerated with a meltable binder like PEG 3000 of Gelucire\textsuperscript{8} 50/13 in a high shear mixer. Polyoxyglycerides, partial glycerides or polysorbates, and


\textsuperscript{66} Andrade, V., et al. (2004). 
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lecithins are some of the lipid excipients used in the melt granulation technique to form self-micro-emulsifying systems80,81.

4.3.5. Supercritical fluid-based method

This method uses lipids for coating drug particles to produce solid dispersions. In this method, the drug and lipid-based excipients are dissolved in an organic solvent and then in supercritical fluid (carbon dioxide)82,83, by elevating the temperature and pressure. The coating process is facilitated by a gradual reduction in pressure and temperature in order to reduce the solubility of the coating material in the fluid and hence precipitate onto the drug particles to form a coating84,85. The solubility of the formulation components in the supercritical fluid and stability of the substance during the process are important considerations of this method. Glyceryl trimeystrate (Dynasan™ 114) and steoaroyl polyoxyglycerides (Gelucire® 50/02) have been used in this process for their controlled-release applications82,83. Sethia and squillante84–86 have formulated solid dispersions of carbamazepine using supercritical carbon dioxide. Vitamin E TPGS and Gelucire® 44/14 were success fully used with this technique (supercritical fluid processing) for enhancement of the bioavailability of carbamazepine. The solid dispersions formulated with TPGS showed enhanced bioavailability of drug when compared to formulations prepared with Gelucire® 44/14 as lipid excipient.

4.4. Characterization of lipid-based formulations

4.4.1. In vitro studies

A preliminary guideline for formulation development and assessment of drug release can be obtained from in vitro studies. Apart from assessing batch-to-batch consistency, these studies also depict the in vitro evaluation of the lipid-based formulation.

In vitro evaluation of lipid-based drug delivery systems can be done with the use of lipid digestion models. In order to assess the performance of an excipient during formulation development and to predict in vivo performance, it is necessary to design an in vitro dissolution testing method. This can be termed as “simulated lipolysis release testing”, which is described in the literature19. The instrument used for studying enzymatic hydrolysis of lipids is a pH-stat titration system, which is depicted in Fig. 3. The basic principle on which this system works requires maintaining a constant pH during a reaction which releases or consumes hydrogen ions. If any deviation is found, it is compensated by the reagent addition.

The model consists of a temperature-controlled vessel (37 °C), which contains a model intestinal fluid, composed of digestion buffer, bile salt (BS) and phospholipid (PL). Into this model a fluid lipid-based formulation is added and to initiate the digestion process pancreatic lipase and co-lipase were added. As the digestion process starts it results in the liberation of fatty acids, causing a transient drop in pH. This drop in pH is quantified by a pH electrode. The pH electrode is coupled to a pH-stat meter controller and autoburette. An equimolar quantity of sodium hydroxide is added to titrate the liberated fatty acids by the autoburette, so as to prevent a change in pH of the digestion medium from a pre-set pH value. By quantifying the rate of sodium hydroxide addition and considering the stoichiometric relationship between fatty acids and sodium hydroxide, the extent of digestion can be quantified. During the digestion process, samples can be withdrawn and separated into a poorly dispersed oil phase, highly dispersed aqueous phase and precipitated pellet phase by centrifugation, as shown in Fig. 4. Quantification of drug in the highly dispersed aqueous phase indicates that drug has not precipitated, from which an assumption can be made with respect to in vivo performance of the lipid-based formulation.

The effect of the concentration of bile salts, calcium and lipase activity on the digestion process was investigated87,88. Results showed that all three parameters had an impact on the initial rate of hydrolysis, whereas the subsequent stages were affected by calcium concentration and lipase activity. To study effect of food for poorly water-soluble drugs, an in vitro lipid digestion model was developed by Christensen and co-workers89. In this model, the transfer of lipophilic drugs from fractionated coconut oil and sesame oil to the aqueous phase was studied. Dahan and Hoffman90 have presented the importance of in vitro lipolysis model for optimizing the oral lipid-based formulations with regard to pre-systemic metabolism in the gut.

4.4.2. In vivo studies

The impact of excipients on the bioavailability and pharmacokinetic profile of drugs can be estimated by designing appropriate in vivo studies. A detailed study of intestinal lymphatic absorption
is required, since lipid-based formulations enhance bioavailability by improving the intestinal uptake of drug. Due to insufficient clinical data and differences in methods and animal models used, studies related to the drug transport by lymphatic system have become difficult. Hence further work has to be carried out to establish an in vivo method and model to predict lymphatic drug transport. A lipid-based formulation of saquinavir mesylate (Fortovase) enhanced the bioavailability of the drug up to three-fold when compared to Invirase (saquinavir in hard gelatin capsules). A study in a mesenteric lymph duct-cannulated rat model was conducted to understand the mechanism for the improved bioavailability with this formulation. The results showed that enhanced solubilization and permeability of the drug in the lipid-rich pre-absorptive intestinal environment was the main reason for the increase bioavailability from Fortovase.

In lymphatic absorption the important step is the association of drug with chylomicrons in the enterocyte. In order to study this, an experimental rat model with blocked chylomicron flow to elucidate the lymphatic transport of Vitamin D₃ was conducted. Upon comparison of these results with the mesenteric lymph duct-cannulated rat model, it showed that the association of drug with chylomicrons led to 75% of the Vitamin D₃ being absorbed through lymphatic uptake. The effect of food (high fatty meal) on the bioavailability of cyclosporine was studied by formulating the drug as Sandimmune Neoral (lipid-based formulation-microemulsion of a surfactant, lipophilic and hydrophilic solvents, and ethanol), and simple emulsion in soft gelatin capsules, and was carried out in healthy human volunteers. The results confirmed that the effect of food was lessened with the lipid-based formulation (Sandimmune Neoral), when compared to a significant effect of food (37% increase in area under the curve) from the simple emulsion. This allowed more flexibility of the lipid-based formulation with regards to their dietary schedule.

4.4.3. In vitro–in vivo correlation (IVIVC)

The in vivo oral bioavailability of two model drugs, griseofulvin and dexamethasone, was predicted by designing an in vitro lipolysis and ex vivo intestinal permeability model. Both drugs had good correlation with their in vitro and in vivo data in regards to lipolysis and absorption. But, the actual in vivo data failed to correlate with the ex vivo permeation studies. Griseofulvin, with limited solubility (5 µg/mL), is influenced by the lipid excipients, the presence of bile salts, phospholipids and lipolytic products in the digestive media. A sound in vitro–in vivo correlation will help to maximize the development potential and commercialization of lipid-based formulations. A shortened drug development period and improved product quality could be achieved by developing a model that correlates the in vitro and in vivo data. Determining the solubility, dissolution, lipolysis of the lipid excipient, intestinal membrane techniques (isolated animal tissue and cell culture models) are various in vitro techniques that can be used to assess lipid-based formulations. Such techniques provide information about specific aspects of the formulation only. But, it is important to know the in vivo interaction and performance of these systems.

Similar to that of in vivo enterocytes, Caco-2 cells produce and secrete chylomicrons on exposure to lipids. More study has to be carried out on the choice of the most suitable in vivo model for assessing the lipid-based formulations.

For initial screening and identifying a prototype formulation, the rat is a reliable model. However, the different anatomy and physiology the rat, such as the lack of a gall bladder and different expression and pattern levels for intestinal enzymes makes correlation of results to human beings challenging. Several lipid-based formulations have been assessed using a dog model, but a poor correlation was observed between dog and human due to differences in GIT physiology like gastric pH and enzymatic profile of enterocytes. In terms of close relation between the anatomy and physiology of the GIT, the pig can be considered as a most suitable non-primate animal model. This model permits the oral administration of full-sized human dose, and even feeding studies can be done. The impact of intestinal absorption and first-pass metabolism of drugs can be studied using the pig model. Hence, in order to establish reliable in vitro–in vivo correlations in lipid-based formulations, selection of the most appropriate in vitro and in vivo models is of primary importance.

5. Conclusions

As many drugs are successfully marketed as lipid-based formulations, the lipid-based drug delivery system (LBDDS) has a wide scope in terms of solubility and bioavailability enhancement. This review focused on the current trends in the field of LBDDS with respect to formulation approaches and their characterization. However, a few limitations of the technology such as the stability of lipid-based formulations, manufacturing methods, the lack of a database considering the solubility of drugs in lipids, indicate that development of proper regulatory guidelines for lipid-based formulations still need to be addressed in depth to advance the technology. Further research has to be carried out in this field regarding the design of a proper in vivo model to correlate the data obtained in vitro studies to the actual in vivo experience. This review provides a summary of lipid-based formulations which may be helpful for the advancement of this technology to obtain a safer, more stable and efficacious drug products.

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