Review Article

NOVEL LIPID CARRIERS FOR ORAL DELIVERY OF LIPOPHILIC DRUGS

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ABSTRACT

Most of the new chemical entities discovered today are highly lipophilic in nature and show poor solubility and membrane permeability resulting in poor oral bioavailability. The need for an effective carrier system led to the development of novel lipid based carriers for enhancing the solubility and bioavailability of such drugs Lipids are fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds. Lipids employed in drug delivery are chemically classified as- Triglycerides, Mono/di Glycerides, Propylene glycol esters, fatty acids and phospholipids. These excipients enhance the drug solubility and bioavailability by either- *in vivo* solubilisation, prolongation of gastric residence time, promotion of intestinal lymphatic transport, affecting membrane permeability, reduced metabolism and efflux activity or combination of these mechanisms. Microemulsion and nanoemulsions, self emulsifying drug delivery system, solid lipid nanoparticles and nanostructured lipid carriers and liposomes are some of the most widely used novel lipid based carriers. Due to their advantages over traditional lipid based systems and ease of scale up and production has led to commercialisation of some of these formulations. These systems have high potential in replacing the traditional lipid based systems in delivery of poorly soluble drugs.

Keywords: Microemulsion, nanoemulsion, self emulsifying drug delivery system, solid lipid nanoparticles, nanostructured lipid carriers, liposomes.

INTRODUCTION

The advent of combinatorial chemistry and high throughput screening has resulted in the rapid identification of many highly potent new chemical entities, substantial fraction of which are highly lipophilic and show poor solubility and membrane permeability. As solubility and permeability are the prerequisites for oral absorption of drugs, many of these compounds exhibit poor and variable bioavailability. Thus, even though these compounds have a powerful pharmacological activity, the clinical efficacy which is expected is not realized.[1,2]

In addition, certain lipophilic drugs show significant first pass extraction as they are candidates for transporters including P-glycoprotein, and for metabolism via cytochrome P450 enzymes. Examples of such drugs include anticancer agents, HIV protease inhibitors, immunosuppressant and cardiovascular drugs. Consequently, the physicochemical properties of the drug in tandem with the physiological environment of the gastrointestinal tract constitute major challenges to successful oral delivery. [2]

Modifying the physicochemical properties of the compound may be used as one of the approach to improve the dissolution rate of the drug. This includes- salt formation and particle size reduction. However, these methods have their own limitations. For instance, salt formation of neutral compounds is not feasible and the synthesis of weak acid and weak base salts may not always be practical. Also, the salts that are formed may convert back to their original acid or base forms leading to aggregation in the gastrointestinal tract. Particle size reduction may not be desirable in situations where handling difficulties and poor wettability are experienced.[3]

Thus, there is a need for the development of effective carrier systems which are capable of overcoming these problems and improving the bioavailability of drugs.

The well known effect of food for improving the bioavailability of many poorly soluble drugs, where the enhanced absorption is often ascribed to the ingested lipid, is ample evidence of the beneficial role that lipids can have on drug absorption. This led to the utilisation of lipid based carriers described below in the formulation of poorly water-soluble drugs (PWSD). In addition lipid based carriers also provide the advantage of taste masking and protection of the active ingredient.[4-6]

Lipids in Drug Delivery

Lipids are fatty acids and their derivatives, and substances related biosynthetically or functionally to these compounds. 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. 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.[7]

Wide availability of lipidic excipients as shown in Fig.1, with specific characteristics offers flexibility of application with respect to improving the bioavailability of poorly water-soluble drugs and manipulating their release profiles. Depending on their chemical composition, lipids are classified as under:

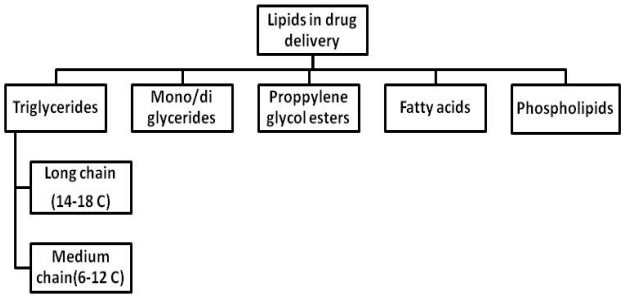

Figure 1: Classification of lipids in drug delivery

Some of the examples of lipids in each category are given below:

i. Triglycerides

Depending on the length of carbon chain, they are classified as Long chain and Medium chain triglycerides-

a. Long chain triglycerides

Eg: Corn oil, Soybean oil, Safflower oil, Olive oil

b. Medium chain triglycerides

Eg: Glyceryl tricaprylate / caprate: Captex®300; Miglyol®810; Miglyol®812; Neobee®M-5

Captex are popular triglycerides and esters and function as solubilizers.

ii. Mono/di glycerides

Commonly known excipients that fall under this category are glyceryl monocaprylocaprate (Capmul® MCM); glyceryl monostearate (Geleol™, Imwitor® 191, Cutina™GMS or Tegin™); glyceryl distearate (Precirol™ ATO 5); glyceryl monooleate (Peceol™); glyceryl monolinoleate (Maisine™ 35-1); glyceryl dibehenate (Compritol® 888 ATO).

iii. Propylene glycol esters

Eg: Propylene glycol monocaprylate (Capmul® PG-8); Propylene glycol monolaurate (Capmul® PG-12, Lauroglycol®)

iv. Fatty acids

Eg. Oleic acid, Palmitic acid, Stearic acid, Linoleic acid

v. Phospholipids

Eg: Phosphatidylcholine, Phosphatidylglycerol, etc.[7]

Mechanism of solubility enhancement by lipidic excipients

As shown in Fig 2, when administered orally, lipidic excipients enhance the solubility and bioavailability of the co-administered drug by one or more of the following mechanisms -

a. *In vivo* solubilisation of drug
b. Prolongation of gastric residence time
c. Promotion of intestinal lymphatic transport
d. Affecting intestinal permeability
e. Reduced metabolism and efflux activity [8]

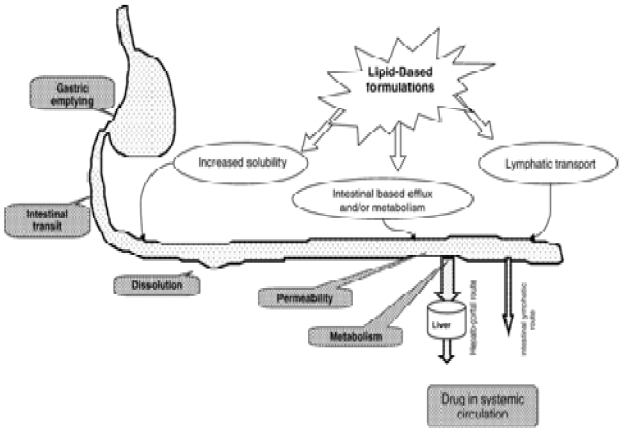

Figure 2: Schematic representation of the critical steps in oral drug absorption and the possible influences of lipid-based formulations[5]

NOVEL LIPID CARRIERS

The traditional lipid based systems are not efficient enough to solve the solubility problems associated with the lipophilic drugs and also these systems are associated with large limitations such as low stability, poor patient compliance etc. Thus there was a need for new carrier systems which led to the development of novel lipid based carriers.

Some of these carriers utilized for solubility enhancement include:

1. Microemulsion and Nanoemulsion
2. Self Emulsifying Drug Delivery System
3. Solid Lipid Nanoparticles and Nanostructured Lipid Carriers
4. Liposomes

1. Microemulsion & Nanoemulsion

In 1959, Schulman *et al*. visualized the existence of small emulsion-like structures by electron microscopy and subsequently coined the term 'microemulsion'. Microemulsions are isotropic, thermodynamically stable transparent (or translucent) systems of oil, water and surfactant, frequently in combination with a co surfactant with a droplet size usually in the range of 20-200 nm. These homogeneous systems are all fluids of low viscosity. Microemulsions as drug delivery vehicle show favourable properties like thermodynamic stability (long shelf-life), easy formation (zero interfacial tension and almost spontaneous formation), optical isotropy, high surface area (high solubilisation capacity), very small droplet size and surfactant-induced permeability enhancement. The small droplets also provide better adherence to membranes and transport drug molecules in a controlled fashion.[9]

Further reduction in droplet size of the internal phase of the microemulsion led to the development of nanoemulsion. Nanoemulsions are thermodynamically stable, transparent (or translucent) dispersions of oil and water stabilized by an interfacial film of surfactant molecules having the droplet size less than 100 nm.[10]

High pressure homogenisation, microfluidization and phase inversion temperature technique are the methods employed for the preparation of nanoemulsions.[11]

The distinction between microemulsion and nanoemulsion is blurred because the description of nanoemulsion is very similar to that of a microemulsion in that they are both oil-in-water dispersions of small droplet size and of narrow droplet size distribution. Although the physical appearance of a nanoemulsion resembles that of a microemulsion in that both systems are transparent (or translucent) and of low viscosity, there is essentially a difference between the two systems namely that a nanoemulsion is, at best, kinetically stable, while a microemulsion is thermodynamically stable. As a consequence many of the nanoemulsions reported in the literature do not possess long term stability as compared to microemulsion. One supposed advantage of a nanoemulsion over a microemulsion is that it requires a lower surfactant concentration for its formation. Pharmaceutical microemulsions, require a surfactant concentration (usually ~20% and higher) to enable optimal drug delivery whereas nanoemulsions can be fabricated with a relatively small surfactant concentration of 3–10%.[11,12]

As seen in Table 1, O/W micro- and nano-emulsion formulations increase the solubility by dissolving the poorly water soluble compounds into an oil phase, thus increasing the dissolution rate and enhancing oral bioavailability. It is also possible for these formulations to raise lymph directivity and avoid hepatic first pass metabolism depending on the kind of oil .[13]

Table 1: Studies investigating the oral bioavailability (BA) of PWSD from microemulsion and nanoemulsion formulations

Compound	Formulation	Study Design	Observation	Ref.
Docetaxel	Microemulsion composed of Capryol 90, Cremophor and Transcutol	Relative BA in rats	BA 3.5 fold higher from microemulsion than Taxotere®	[14]
Fenofibrate	Microemulsion composed of Capryol 90, Cremophore EL, Transcutol P	Relative BA in dogs	BA 1.63 fold higher from microemulsion than Lipanthy® capsule	[15]
Ibuprofen	Microemulsion composed of medium chain fatty acid triglyceride MCT, diglyceryl monooleate, polyoxyethylene hydrogenated castor oil 40	Relative BA in rats	BA 8.7 fold higher from microemulsion	[16]
Candesartan cilexetil	Nanoemulsion composed of Soybean oil, Solutol HS-15 and Tween 80	Relative BA in rats	BA 10 fold higher from nanoemulsion	[17]
Ezetimibe	Nanoemulsion composed of Capryol 90, Tween 20 , PEG 400	Relative BA in rats	BA 4.77 fold higher from nanoemulsion	[18]
Ramipril	Nanoemulsion composed of Sefsol 218 , Tween 80 and Carbitol	Relative BA in rats	BA 2.9 fold higher from nanoemulsion	[10]
Silymarin	Nanoemulsion composed of Sefsol 218, Tween 80 and ethanol	Relative BA in rats	BA 2 fold higher from nanoemulsion than SILYBON® suspension	[19]

2. Self Emulsifying Drug Delivery System (SEDDS)

Although the nanosized or submicronic emulsions improve the GI absorption of hydrophobic drugs, the use of these emulsions in oral delivery is limited, owing to various limitations. These include- poor palatability due to their lipidic composition or consumption of a higher volume to achieve the necessary therapeutic concentration for certain drugs which have limited solubility in all the oils with pharmaceutical acceptability for eg. Carbamazepine, Quercetin. This severely limits patient compliance. Also, as these emulsions have high water content, they cannot be delivered through soft gelatin, hard gelatin or hydroxypropylmethylcellulose capsules and the water content of these emulsions may promote hydrolysis and/or precipitation of certain drugs on long-term storage, which could affect their utility in oral delivery.[11]

This led to the development of Self emulsifying drug delivery system.

Self-emulsifying formulations comprise of isotropic mixtures of natural or synthetic oils with lipophilic or hydrophilic surfactants and co-solvent(s) which spontaneously emulsify when exposed to the fluids of the GIT to form oil-in-water emulsions, microemulsions or nanoemulsions. Self emulsifying formulations also provide the advantage of increased drug loading capacity when compared with lipid solutions, as the solubility of poorly water-soluble drugs with intermediate partition coefficients (2<log P<4) are typically low in natural lipids and much greater in amphiphilic surfactants, co-surfactants and co-solvents. Rapid emulsification of these systems under mild agitation and in the presence of aqueous media of the GI fluids generates a high surface area of interaction between the formulation and the GI fluids, thus improving the rate and extent of absorption as seen in table 2 and resulting in more reproducible blood time profiles.[20-22]

There are few issues associated with liquid SEDDS when presented in capsules, such as incompatibility of components with the capsule shell in the long term, precipitation of drugs during fabrication and storage at low temperature and critical method of production.[10]

To overcome the limitations associated with liquid SEDDS, the concept of solid SEDDS was developed. Various techniques, such as spray drying, freeze drying and adsorption on carriers, can be employed to convert liquid SEDDS into solid SEDDS depending on the content of oily excipients in the formulation, properties of active pharmaceutical ingredients such as solubility, heat stability and compatibility with other ingredients. These systems may then be incorporated into capsules directly, or transformed into granules, pellets or powders for dry filled capsules as well as tablet preparations.[11, 14]

Depending on the droplet size of emulsion formed, we have different types of self emulsifying formulations namely:

- Self-emulsifying drug delivery systems (SEDDS)
- Self-microemulsifying drug delivery systems (SMEDDS)
- Self-nanoemulsifying drug delivery systems (SNEDDS)

SEDDS, SMEDDS and SNEDDS are mainly distinguished by the size of the oil droplet formed on emulsification.

SEDDS typically produce opaque emulsions with a droplet size between 100 and 300 nm while SMEDDS form transparent micro emulsions with a droplet size of less than 100 nm. Also the concentration of oil in SMEDDS is less than 20 % as compared to 40-80% in SEDDS.[2, 21]

SNEDDS is a recent term construing the globule size range less than 50 nm.[20, 21, 22]

Table 2: Studies investigating the oral bioavailability (BA) of PWSD from SEDDS, SMEDDS and SNEDDS formulations

Compound	Formulation	Study Design	Observation	Ref.
Coenzyme Q10	SEDDS composed of Labrafil M 1944, Labrafil M 2125, Labrasol, Lauroglycol FCC and Capryol 90	Relative BA in rats	BA 2 fold higher from SEDDS	[23]
Phenytoin	SEDDS composed of Labrasol, Transcutol and Labrafac	Relative BA in rats	BA 2.3 fold higher from SEDDS	[24]
Curcumin	SMEDDS composed of Labrafac PG and Capryol 90 Cremophor EL and Labrasol	Relative BA in rats	BA 13.93 fold higher from SMEDDS	[25]
9-nitro camptothecin	SMEDDS composed of ethyloleat, Tween-80, PEG-400	Relative BA in rats	BA 2.18 fold higher from SMEDDS	[26]
Oridonin	SMEDDS composed of Maisine 35-1, Labrafac CC , Cremopher EL, and Transcutol P	Relative BA in rats	BA 2.2 fold higher from SMEDDS	[27]
Lutein	SNEDDS composed of Phosphatidylcholine (Phosal 53 MCT) Labrasol and Transcutol-HP	Relative BA in rabbits	BA from SMEDDS 2.86-folds higher compared with commercial powder, and 12.32-folds higher compared with powder drug	[28]
Persimmon (Diospyros kaki) leaf extract	SNEDDS composed of Cremophor EL, Transcutol P, Labrafil M 1944 CS	Relative BA in dogs	Compared with the commercial tablets, the AUC of both quercetin and kaempferol, which are representative active flavonoids of PLE, was increased by 1.5-fold and 1.6-fold respectively	[29]
Talinolol	SNEDDS composed of Brij-721 ethanolic solution, triacetin	Relative BA in rats	BA 1.41 fold higher from SNEDDS	[30]

3. Solid Lipid Nanoparticle (SLN) & Nanostructured Lipid Carriers (NLCs)

Solid lipid nanoparticles (SLN) are produced by replacing the oil of an o/w emulsion by a solid lipid or a blend of solid lipids. The lipid particle matrix remains solid at both room and body temperature allowing drug release over prolonged period of time. SLN are composed of 0.1 to 30% (w/w) of solid lipid dispersed in an aqueous medium having mean particle size in the submicron range of about 40nm to 1000nm. They are biodegradable, non-toxic and stable against coalescence, hydrolysis and particle growth.

SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the surfactants. The drug may be incorporated into the SLNs in different ways i.e. into a homogeneous matrix or into shells or as a lipid-coated core. [4, 31, 32]

Some common problems associated with SLN include- drug expulsion, low loading capacity, risk of gelation and drug leakage during storage caused by lipid polymorphism.[31]

The nanostructured lipid carriers (NLCs) are regarded as the second-generation of lipid nanoparticles and have been developed to overcome the limitations associated with SLN. They are produced by controlled mixing of solid lipids with spatially incompatible liquid lipids which leads to special nanostructure with improved properties for drug loading, modulation of the drug release profile and stable drug incorporation during storage. Depending on the method of preparation and the composition of lipid blend, NLCs with different structures are obtained, i.e., the imperfect, amorphous and multiple components. Admixture of liquid lipids with solid lipids leads to a less ordered inner structure due to which the drug molecules are accommodated in between lipid layers and/or fatty acid chains. Thus, NLCs are considered a smarter generation of nanoparticles.[31, 33]

The absorption-enhancing effect of orally administered nanoparticles may be attributed to the adhesion of the particles to the gut wall. The adhesion of lipid nanoparticles to the mucus can improve the residence time and contact of the drug with the underlying epithelium, thus increasing the concentration gradient. Also, the protection of the drug by the lipids from chemicals and enzymatic degradation, delay the in vivo metabolism[31].

Due to their protective properties, SLNs and NLCs are of particular interest for peptide and protein delivery by oral route.[34]

A number of examples of studies of SLN and NLC formulations are summarized in table 3.

4. Liposomes

Liposomes are vesicular systems in which lipid bilayer structures are present with aqueous volume entirely enclosed by a membrane, composed of lipid molecules. Liposomes are the most promising, broadly applicable, and highly researched of all novel delivery systems as they offer temporal control of drug release and site

specific drug delivery for a wide range of drugs with different physiochemical properties.[37]

When given orally, liposomes may provide increased solubility of their load and protect it from the hostile environment of the gastrointestinal tract. In addition, due to the similarity between liposomal lipid bilayers and biomembranes and their relatively small size, liposomes significantly facilitate oral absorption of drugs as seen in table 4.[38]

Table 3: Studies investigating the oral bioavailability (BA) of PWSD from SLN and NLC formulations

Compound	Formulation	Study Design	Observation	Ref.
Candesartan cilexetil	SLN composed of Tween 80 glycerol monostearate Soybean lecithin (S100).	Relative BA in rats	BA 12 fold higher from SLN	[33]
Quercetin	SLN composed of Glyceryl monostearate Soya lecithin Tween-80 and PEG 400.	Relative BA in rats	BA 5.71 fold higher from SLN	[34]
Etoposide	NLC composed of monostearin soybean oil soya lecithin PEG-40 DSPE-PEG.	Relative BA in rats	BA 3.5 fold higher from NLC	[35]
Vinpocetine	NLC composed of Compritol 888 ATO, Miglyol812N, SolutolHS-15 and Lecithin.	Relative BA in rats	BA 3.2 fold higher from NLC	[36]

Table 4: Studies investigating the oral bioavailability (BA) of PWSD from liposome formulations

Compound	Formulation	Study Design	Observation	Ref.
Zaleplon	Phospholipon 90H, Cholesterol, stearylamine and mannitol	Relative BA in rats	BA 2-5 fold higher from proliposomes	[39]
Vinpocetine	Soybean phosphatidylcholine, Cholesterol and Sorbitol	Relative BA in rabbits	BA 3.5 fold higher from proliposomes	[40]
Silymarin	phospholipid 82% (w/w) of the phosphatidyl and Mannitol	Relative BA in dogs	BA 3.7 fold higher from proliposomes	[41]

The underlying mechanisms for enhancement of oral bioavailability of poorly soluble drugs by liposomes are stated as under:

(i) By virtue of the surfactant property of the phospholipids, they can reduce the interfacial barrier and provide intimate contact with epithelial cell membrane thus favouring the partitioning of drug into the hydrophobic domain of the cell membrane.

(ii) Fusion of the liposomes with the epithelial cells by endocytosis might be responsible for the augment in absorption across GI membrane.

(iii) Direct transfer of liposomes formed at the vicinity of the GI tract may lead to an improved bioavailability due to avoidance of first pass metabolism.[39]

Due to erratic and unpredictable absorption profiles, liposomes have limited success rate in oral delivery of drugs. Also liposomes suffer from several stability problems such as sedimentation, aggregation, fusion, phospholipid hydrolysis, and/or oxidation. In addition, large scale production of liposome remains unresolved. The proliposome tactic has provided a major breakthrough in resolving these issues. Proliposomes are the dry powder formulations containing water soluble carrier particles coated with phospholipids and can be reconstituted to form liposomal dispersion on brief agitation in aqueous media. Being dry and free-flowing, the proliposomes offer ease of distribution, transfer, measuring and storage which makes it a versatile delivery system. Also, the liposomes formed after the dispersion is similar to conventional liposomes and more uniform in size and being available in the dry form, they can be formulated into conventional dosage forms such as tablets and capsules.[39, 40]

CONCLUSION

As seen above novel lipid based carriers are highly efficient in enhancing the solubility and bioavailability of poorly soluble lipophilic moieties. These systems can not only be used for the new chemical entities but can also be applied to the existing drug molecules showing poor and variable bioavailability. Realising their advantages over the traditional lipid based carriers and ease of scale up and large scale production of these systems, the industries have adopted these novel carriers for commercial use.

With the novel drug delivery system growing rapidly throughout the world, it is not far when the traditional lipid based systems will be replaced by the novel lipid based carriers ensuring better drug delivery and thus better patient compliance.

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