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Silica-Lipid Hybrid Microparticles for Improved Bioavailability of Bcs Class IV Drugs

Vijay kumar Nagabandi*[1], Swapna Sambaraj[2]

[1]M. Pharm., Ph.D., Assistant Professor, Department of Pharmaceutics, St. Peter's Institute of Pharmaceutical Sciences, Vidyanagar, Hanamkonda, Andhrapradesh – 506001, India.
[2]M. Pharm., Department of Industrial Pharmacy, St. Peter's Institute of Pharmaceutical Sciences, Vidyanagar, Hanamkonda, Andhrapradesh – 506001, India.

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Address for Correspondence
Department of Pharmaceutics
St. Peter's Institute of Pharmaceutical Sciences
Vidyanagar, Hanamkonda, Andhra Pradesh, India - 506001.
Tel. +91-9676000096.
E-mail: vijaybpharm@gmail.com

ABSTRACT

The main objective of the current review is to cover the overview of silica lipid hybrid microparticles. Lipid-based delivery systems recognized as a potential strategy for improving the oral absorption. Clinical applications of many lipid-based formulations are limited by the lack of clear guidelines of incomplete understanding of absorption mechanism and *in vitro*, *in vivo* formulation performance. Withstanding these problems, the availability of 2-4% oral lipid based products in the pharmaceutical market worldwide has supported in addressing low bioavailability of poorly soluble drugs. A novel silica-lipid hybrid microparticulate system is used for enhancing the oral absorption of low solubility and low permeability of (BCS Class IV) drugs. It describes the systematic *in vitro* characterization of dissolution and lipolysis properties. Silica-lipid hybrid microparticles include the drug solubilising effect of dispersed lipids and stabilizing effect of hydrophilic silica particles to increase drug solubilisation, which leads to enhanced oral bioavailability. Hence, silica lipid microparticles can be used to enhance the bioavailability of BCS class IV drugs effectively.

Keywords: Silica lipid, Bioavailability, Permeability, Microparticles.

INTRODUCTION

Of all the drug delivery systems oral route is the most convenient and non-invasive method of drug administration which receives the highest degree of patient compliance. For a drug substance that to be well absorbed following oral administration, it has to: (i) be sufficiently soluble in the gastrointestinal fluids and (ii) easily

permeate across the GI membrane without undergoing significant degradation or elimination mediated by the GI enzymes and enterocyte transporters[1].

According to recent estimates, nearly 30% of the oral immediate-release drug products and 40-70% of the newly discovered chemical entities are poorly soluble in water[2].

Drugs with poor aqueous solubility and dissolution properties are not suitable for oral delivery using conventional tablet formulations as it produces low and variable bioavailability, which leads to erratic biological effects[3].

In order to improve the solubility-limited bioavailability, lipid-based formulations have emerged as an effective and versatile solubilisation technology[4,5].

Successful therapeutic applications of oral lipid-based formulations, that accounted for 2-4% of the pharmaceutical market worldwide. It suggests the need for more intensive and systematic studies on lipid-based systems to foster the growth of viable formulations of poorly water-soluble drugs.

FORMULATION OF POORLY WATER-SOLUBLE DRUGS

Biopharmaceutical classification of drug substances

As described in Biopharmaceutics Classification Scheme (BCS), based on their aqueous solubility and intestinal permeability properties, drug substances are categorized into four classes *i.e.* BCS Class I to IV as summarised in Table 1.1A.

This classification scheme is to determine the importance of solubility and permeability on drug absorption. The factors that govern the rate and extent of drug absorption include[6],

(i) Solubility: a drug substance is considered "highly soluble" when the highest dose strength is soluble in ≤ 250 ml of aqueous media over a pH range of 1 to 7.5;

(ii) Permeability: a drug substance is considered "highly permeable" when the extent of drug absorption in humans is ≥ 90% of an administered dose;

(iii) Dissolution rate: a drug product is considered to be "rapidly dissolving" when > 85% of the labelled amount of drug substance dissolves within 30 min using the United States Pharmacopoeial (USP) Apparatus I or II in a volume of less than 900 ml of buffer solution.

BCS scheme implemented by the United States Food and Drug Administration (USFDA) as an industrial guidance to justify bio waiver through bioequivalence testing of immediate-release solid dosage forms for highly soluble–highly permeable drugs.

Poorly water-soluble drug compounds (BCS Class II and IV) are those with a dose/solubility ratio of > 250 ml or with an aqueous solubility of < 100 µg/ml[7]. 'Highly permeable' drugs are the compounds; with an oral dose that exhibit ≥ 90% absorption. The enterocyte transporter-enzyme functions (uptake or efflux effects) are taken into consideration in addition to lipophilicity properties.

Considering the BCS, Log *P* is the logarithm of octanol-water partition coefficient, which is widely used as a quantitative descriptor for lipophilicity.

Wu and Benet suggested a novel Biopharmaceutics Drug Disposition Classification System (BDDCS) (Table 1.1B) to indicate the overall exposure of drugs following oral administration, the parameter permeability is replaced with 'first-pass metabolism'.

Oral formulation strategies for poorly water-soluble drugs

(a) Particle size reduction/ micronisation

According to the Noyes-Whitney principle, increased rate of drug dissolution is due to an increased wetted surface area or reduced particle size. This has exemplified for poorly water-soluble drug models such as indomethacin, fenofibrate[8], ibuprofen, itraconazole, and ketoconazole. (Table 1.2)

(b) Solid solutions/ dispersions as supersaturating drug delivery systems

Solid dispersions are produced by the dispersion of drugs in a hydrophilic or water soluble matrix in a solid state. These are *eutectic dispersions*, in which drugs are presented in solid solution or microcrystalline state, where the fraction of drugs are dispersed in the matrix[9].

Improvement in drug dissolution by solid dispersion attain in two ways:

(i) The inclusion of a polymer-based stabilizer such as: (e.g. PEG, HPMC) is an effective method to maintain the supersaturation state or to delay precipitation (*i.e.* 'crystal growth') of drugs in the GI fluids.

(ii) Typically, a surface-active stabiliser (e.g. SLS, PEG-polysorbate 80 mixture) is included in a solid dispersion system to prevent the formation of a drug-rich hydrophobic barrier on the surface of the dissolving matrix[4, 5]

This system presents the drugs in high energy, thermodynamically unstable forms (metastable or amorphous) and that provides accelerated solubility and dissolution in GIT. It also enhances the intestinal uptake of drug molecules down the concentration gradient.

(c) Surfactant/cosolvent system

These are used alone or in combination to increase the solubilisation power of aqueous medium.

(i) These are amphiphilic agents which improves drug solubility and dissolution by lowering the surface tension or by forming micelles at concentrations exceeding their critical micelle concentrations (normally in the range of 0.05–0.1% for most surfactants) (Das *et al*. 2006)

E.g. sodium lauryl sulphate (anionic), polysorbates, polyoxyethylated castor oil (non-ionic).

(ii) The commercialization of products is mainly based on non-ionic surfactants, as it increases the acceptability for oral administration and the risk benefit ratio helps in using of surfactants in chronic products.

E.g. HIV antiretroviral drugs, including amprenavir (Agenerase®, GSK), lopinavir/ritonavir tablet (Kaletra®, Soliqs), and ritonavir (Norvir®, Abbott Laboratories), (polyoxyethylated castor oil, Cremophor) [4, 5]

(iii) Pharmaceutically employed cosolvents are water-miscible organic solvents which can confer high solubility to hydrophobic solutes via specific molecular interactions (such as hydrogen bonding) [9]

E.g. ethanol, glycerin, polyethylene glycol (PEG) and propylene glycol, nifedipine (Procardia®, Pfizer) [10]

(d) Cyclodextrins

Cyclodextrins (CDs) are starch-derived cyclic oligosaccharides with a hydrophilic exterior and hydrophobic interior, which may contain six (α-CD), seven (β-CD), eight (γ-CD) or more α-D-glucopyranose units[11]

The major mechanism which includes:

(i) CDs with the formation of non-covalent inclusion complexes increase the apparent solubility and dissolution of drugs.

(ii) CDs may also form non inclusion-based complexes and act as a surfactant, supersaturation stabiliser and precipitation inhibitor in the aqueous environment.

(iii) Drug release from covalently bound CD-drug conjugates is induced by enzymatic degradation and is useful for colon targeted drug delivery. Dissociation of drug molecules from CD-drug complex is triggered by aqueous dilution, replacement by dietary lipids or close affinity of drug molecules towards biological membranes (oral mucosal).

Commercialized oral CD-based products include: e.g. a α-CD-based cefotiam-hexetil HCl tablet (Pansporin T®, Takeda), a β-CD-based nicotine sublingual tablet (Nicorette®, Pfizer), a 2-hydroxypropyl-β-CD-based itraconazole solution (Sporanox® oral solution, Janssen Pharmaceutica).

(iv) For targeted delivery, increased complexation efficacy and prolonged therapeutic effect of poorly water soluble drugs, the combined use of CDs and surfactants, liposomes have been investigated.

(e) Crystal habit modification

(i) A solid drug substance may exist in one or more crystalline form (*i.e.* polymorphs) which exhibits different physicochemical properties such as melting point and stability, has impact on solubility and dissolution rate[10].

(ii) The important consideration while selecting a polymorph for formulation is to balance between manufacturability, solubility and stability of a compound. so, the potency is maintained over shelf-life period.

(iii) With the supersaturation or recrystallisation of drugs from different solvents, metastable crystals are formed in the presence or absence of surfactants and polymers[10].

Abbott Laboratories reformulated Norvir® in the lower energy polymorph form (still in solution-filled gel capsules), which requires refrigeration due to thermal instability of the crystals.

(f) Prodrugs:

(i) Prodrugs are biologically inactive compounds that undergoes transformation into the active parent drug via., chemical or enzymatic reactions.

(ii) It involves chemical modification of the pharmacophore by adding a polar (either ionisable or non-ionisable) functional group. It should always be balance between the aqueous solubility and the membrane permeability to ensure adequate intraluminal solubilisation and intestinal uptake[12].

It is a suitable approach for drugs requiring high doses of administration and those with poor aqueous and lipid soluble drugs.

E.g. fosamprenavir calcium (Lexiva® or Telzir®, GlaxoSmithKline. This prodrug formulation showed higher solubility than the parent drug (*i.e.* ~10 times increased solubility)

(iii) Besides solubility enhancement, prodrug masks the local GI irritation by the non-ionisable, sulfoxide prodrug of sulindac sulfide (Clinoril®, Merck), which is a non-steroidal anti-inflammatory drug (NSAID)[13].

(g) Salt formation

(i) Most of the drug pharmacopoeial monographs demonstrates a solubility of >10 mg/ml are hydrochloride, sulphate, maleate and citrate salts of basic drugs (e.g. chlorpromazine HCl and morphine sulphate);

and potassium, calcium and sodium salts of acidic drugs (e.g. dicloxacillin sodium and losartan potassium).

(ii) If a drug molecule is ionisable within GI pH range of 1–9 and includes chemical conversion of parent unionized drug into crystalline salt form and exhibits a strong pH dependency of the distribution coefficient (log *D*) is the most fundamental approach for improving the solubility and dissolution rate of drug.

(h) Lipid-based formulations

Among the four classes of drugs, BCS Class IV drugs are likely to benefit more especially by lipid dosage forms due to their miscibility in lipids and significance of food effects in enhancing solubilisation and absorption *in vivo*

(i) Based on the composition of lipids and surfactants, these are broadly classified into Lipid Formulation Classification System (LFCS) Type I (oil based), Type II (oil and lipophilic surfactant-based), Type III (oil and hydrophilic surfactant-based) and Type IV (surfactant and cosolvent-based) formulations.

(ii) Lipid-based formulations, are those which increases the drug bioavailability by presenting the drug in a molecularly dissolved state during GI transit, as well as initiating a series of physiological responses (e.g. increased biliary secretions) and biochemical changes (e.g. increased intestinal permeability) in the GI tract which favours drug absorption[14].

Lipid-based carriers for oral delivery of poorly water-soluble drugs

Lipid excipients include: solutions, suspensions, emulsions (liquid or dry form), micellar systems, solid lipid particles, liquid crystalline phase carriers, liposomes and various self-emulsifying systems.

Applications of these formulations mainly depend on nature of processing in the GI lumen, physicochemical properties of lipid excipients and their compatibility with the drug molecules.

Types of lipid excipients

Commercially available lipid excipients are categorised into the following classes based on manufacturing methods and chemical compositions (Table 1.3)

(a) Fatty acids

These are monocarboxylic acid derivatives of saturated or unsaturated aliphatic hydrocarbons.

(i) Saturated FA with ≤ 8 carbons in the chain length are flowable liquids, where as those with ≥ 10 carbons are semi-solids at room temperature.

(ii) Fatty acids are used as a solubiliser in pharmaceutical formulations.

(iii) Instability of lipids can be minimized resulted from oxidative reactions which include:

(a) Purification to remove the impurities
(b) Addition of antioxidant
(c) Hydrogenation to decrease the number of carbon-carbon double bonds
(d) Maintaining a pH of 6.5 during processing and in final product
(e) Protection from light and excessive heat

(iv) Lipids containing unsaturated FA are much prone to oxidation, which is catalysed by impurities such as metal ions, peroxides, and photochemical sensitizers (e.g. chlorophyll and riboflavin); which is

identified by the unpleasant tastes and odours of the 'rancid' lipids.

(v) Due to adequate solvent capacity, appreciable self-emulsifying efficiency in aqueous media and high fluidity, natural MCT oils (e.g. Miglyol and Capmul) have gained much importance in formulating drugs of intermediate lipophilicity (log P < 5) in comparison to LCT.

(vi) Miglyol 812 (TG) is a mixture of saturated caprylic/capric (C8/C12) triglycerides, due to its resistance against oxidative decomposition, it is preferred for developing a stable formulation[16].

(vii) Capmul MCM shows unique amphiphilic character, in which it maintains a hydriphile-lipophile balance (HLB) of 5-6 and is often used as solubiliser, emulsifier.

(viii) Oleic acid potentiates lymphatic uptake of lipophilic drugs through the formation of chylomicrons (80–1000 nm) in the enterocytes[17].

(b) Natural oils and fats

Lipids are the mixtures of naturally occurring triglycerides (TG) which contains FA of different chain length and degree of unsaturation.

Depending upon hydrocarbon chain length of fatty acid, oils and fats can be classified as:

(a) short-chain triglycerides SCT (< 5 carbons).

(b) medium-chain triglycerides, MCT (6–12 carbons)

(c) long-chain triglycerides, LCT (> 12 carbons)

They can be used as solubilisers in oral formulation products.

(c) Emulsifiers

(i) Lecithins are heterogenous materials which are extracted from biological sources (e.g. soybean, eggs, sunflower seeds) due to their high surface active properties and biodegradability, these are extensively used in stabilizing oil-water systems[18].

(ii) Saturated lecithins showed higher risk of haemolysis that used in intravenous emulsions when compared with unsaturated lecithins.

(iii) Due to least haemolytic risk, Soybean lecithin is selected for the current oral formulation development in which the lecithin component undergoes enzymatic digestion prior to intestinal absorption.

(iv) The hydrophile-lipophile balance (HLB) is a measure of the relative hydrophilicity and lipophilicity of amphiphilic molecules. compounds with HLB values < 12 are hydrophobic, whereas those with values > 12 are hydrophilic

(d) Semi-synthetic mono-, di-, and triglycerides

(i) Semi-synthetic mono-, di-, and triglycerides (MG, DG, and TG) are fractioned glycreides when compared to naturally occurring oils and fats, these have less variability and specified range of acceptability in their compositions.

(ii) Due to specific compositions and improved uniformity, it attains greater pharmaceutical applications, including emulsifiers, suspending, wetting agents and solubilising agents.

E.g. Fractionated coconut oil (e.g. Miglyol 810 and Captex 300), contains ≥ 95% MCT and suitably used as an oily excipient in soft gelatin encapsulated products such as Advil®, Pfizer/Wyeth (ibuprofen) and Robitussin®, Pfizer/Wyeth (guiafenisin).

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

(i) These are chemically modified mixtures of MG, DG and TG with fatty acid esters of PEG are used as emulsifier in self-emulsifying systems, fluid or thermo-softening semi-solid solubilising vehicles, surfactants and wetting agents.

(ii) Thermo-softening semisolids require melting at(26–70°C) is then filled into hard gelatin capsules before they can be used as a solubilising or suspending agent.

(iii) The fluid excipients with the addition of colloidal silicon dioxide modified to form thixotropic formulations useful for preparing lipid suspensions of solid drugs.

(f) Polyglyceryl fatty acid ester

(i) These acts as crystallization inhibitors, solubilisers, vehicles, emulsifiers and surfactants.

(ii) These are made by linking a chain of glycerol molecules via., ether linkages, followed by esterification with one or more FA molecules.

(iii) Hydrophilicity mainly depends on number of free hydroxyl groups and the polyglycerol chain length.

(g) Stabilisers/ solid carriers

(i) A solid carrier is used as an excipient which is incorporated into an emulsion system for encapsulating lipids and conversion into dry state.

(ii) Water soluble carriers (e.g. gelatine, sugars, glycine, povidone, and HPMC), water-insoluble carriers (e.g. magnesium alumino metasilicate, Neusilin and colloidal silica) are mostly used.

(iii) Colloidal silica is commonly used as pharmaceutical/food excipient approved by the Therapeutic Goods Administration without specific restriction on the daily oral dose.

(iv) In the current research work, hydrophilic fumed silica (Aerosil 380) is used as an insoluble nanoparticulate stabiliser and solid carrier for lipid encapsulation.

(h) Cholesterol and phospholipids

(i) Phospholipids can be subdivided into negatively charged lipids (e.g. phosphatidic acid and phosphatidyl glycerol), Zwitterions (e.g. phosphatidyl choline and phosphatidyl ethanolamine) or a mixture of both (e.g. L-α- lecithin and egg lecithin).

(ii) The use of charged phospholipids may confer stability to the emulsion and liposomal systems by preventing droplet aggregation and fusion.

(iii) Lipids are classified into two groups: (Table 1.4) *polar lipids* (which interact with water) and *non-polar lipids* (which do not interact with water).

Gastrointestinal processing of lipids and drug transport

(i) Digestion of the lipid excipients mediated by the GI enzymes have a crucial impact on the intra luminal release and solubilisation state of the compound.

(ii) It is essential to understand the fundamental process of lipid digestion and the possible drug transport pathways across the enterocytes.

(iii) Digestion of lipids is mainly catalysed by the water-soluble enzymes, lipases, producing the lipid monomers of FA, MG, and to a lesser extent, glycerols (Table 1.5). Other enzymes which are pancreatic carboxyl esterase, a non-specific catalyst for non-emulsified substrates, and phospholipase

A2, which is responsible mainly for the digestion of phospholipids (PL)[14,17].

Gastric processing of lipids

Physiological aspects

(i) The digestion of lipids (up to 30%) is initiated in the stomach by gastric lipase and lingual lipase. The ingested lipids are prone to emulsification facilitated by the gastric shear forces, the presence of membrane-derived PL and the generated amphiphilic lipolysis products.

(ii) The FA products potentially re-organise into peripheral particles which entrap the gastric lipase that typically acts at the lipid-water interface. However, the FA-entrapped gastric lipase found to retain its enzymatic activity following gastric emptying.

Impact on drug delivery

(i) Encapsulation of poorly water-soluble drugs in lipids have several advantages.

(a) Drug compounds are dispersed in lipid phases. This inherently eliminate the need for pre-absorptive drug dissolution in the GI fluids, and the intraluminal processing of lipids[20]. (Figure 1.1A)

(b) Presence of lipids in the intestine induce a dose-dependent feedback inhibition of gastric emptying, which result in increase the drug solubilisation degree in stomach.

1.1(A) Gastric lipolysis catalysed by gastric lipase, which is gradually inhibited by the accumulated digestion products (mainly DG and FA) at the lipid droplet surfaces (scanning electron micrographs adapted from [21]

1.1(B) Duodenal lipolysis of lipid droplets emptied from the stomach catalysed by pancreatic lipase-colipase complexes, which results in the formation of a highly solubilising lipophilic microenvironment that subsequently facilitates drug transport across the unstirred water layer and enterocytes (photomicrographs adapted from[20]

(ii) The slow down in gastric emptying has been suggested to be a means of controlling and prolonging the transit time of drugs at the absorption site, thereby increasing the drug bioavailability[22].

Intestinal processing of lipids

Physiological aspects

(i) Upon entry into the duodenum, the partially digested lipid substrates (*i.e.* a mixture of TG, DG, MG and FA) stimulate the secretion of bile salts (BS) and biliary-derived lipids (PL and cholesterol) from the gall-bladder, as well as the release of lipase enzymes from the pancreas.

(ii) The endogenous BS/PL components further reduce the droplet sizes and enhance the colloidal stability of the lipid droplets

(iii) Pancreatic lipase, plays a major role in completing the hydrolysis of insoluble lipid substrates in a basic environment.

(iv) For each TG molecule hydrolysed, one molecule of 2-MG and two molecules of FA (with traces of 1-MG and glycerols) are produced.

(v) Lipolysis of TG and DG produces the less hydrophobic lipid monomers (FA and MG) which accumulate at the droplet surface as the liquid crystalline vesicles, which rapidly re-organise to form lipid-BS/PL mixed micelles.

Impact on drug delivery

(i) As lipid droplets digestion progresses, the liquid crystalline lamellae and the colloidal species formed serve as the key

lipophilic reservoirs to keep the drug molecules solubilised in the bulk aqueous phase, and ultimately reach the intestinal absorptive cells (Figure 1.1B).

(ii) Solubilisation in BS micelles increases the aqueous concentration of FA and MG. Such saturation state in turn creates a concentration gradient that drives diffusion of the micellar structures across the UWL, and induces intestinal uptake of the lipolysis products.

Intestinal uptake

Physiological aspects

(i) The apical brush border membrane of the enterocytes is packed with microvilli (~100 nm), where the spaces between the microvilli range from 5–20 nm . The absorption of lipolysis products has long been thought to be a concentration gradient-driven process in which the FA and MG monomers are absorbed predominantly via passive diffusion across the enterocytes.

(ii) Besides the uptake transporter systems, embedded in the apical membrane are the multidrug efflux proteins (particularly P-glycoprotein, P-gp) and the metabolising enzymes (primarily the cytochrome P450 3A enzymes, CYP3A). These act to control the uptake and elimination of a wide range of lipophilic and amphiphatic xenobiotics.

Impact on drug delivery

(i) Using excised intestinal segments and Caco-2 cell lines. (Swenson *et al*.1994, Collnot *et al*. 2006). It has been suggested that the digested lipids and BS components enhances drug permeation by:

(*a*) increasing the intestinal membrane fluidity

(*b*) disrupting the integrity of the tight junctions

(ii) The inhibitory effects of various lipid and surfactant excipients on the intestinal P-gp efflux and CYP3A metabolising systems, which eventually leads to an enhanced drug bioavailability

Types of lipid-based formulations and factors affecting drug absorption

Some potential mechanisms by which lipid-based vehicles enhance the oral absorption of poorly water-soluble drugs

(i) Presence of drugs stable in the molecularly dispersed/ dissolved state.

(ii) Increased GI residence time.

(iii) Improved intestinal solubilising capacity.

(iv) Down regulation of the intestinal efflux and metabolism functions.

(v) Intestinal lymphatic transport, which minimises the first-pass metabolism effect.

Lipid solutions and suspensions

(i) Both lipid solutions and suspensions are relatively simple approaches shown to enhance oral bioavailability of many lipophilic drugs

(ii) Lipid solutions are oily vehicles which contain the drug substance in a fully solubilised form, whereas lipid suspensions are two-phase systems in which the finely divided drug substance is dispersed in the lipid matrix.

(iii) For e.g., cinnarizine when administered as a lipid (oleic acid) solution, has been reported to produce approximately 3- and 4-fold higher maximum plasma concentration (Cmax) and bioavailability (BA), respectively, in comparison with the conventional tablet formulation[23].

Lipid emulsions/ microemulsions

(i) The presence of lipid vehicles in the emulsified form has proved to be effective in increasing the rate of drug release and/or the rate of lipid digestion via an increased total surface area.

(ii) Microemulsions used for oral delivery of lipophilic drugs are thermodynamically stable, isotropically clear dispersions of oil droplets stabilised by surfactants/ emulsifiers or co-surfactants in an aqueous continuous phase[24].

Dry emulsions

(i) The transformation of liquid emulsions into the solid state by spray-drying, this was followed by lyophilisation and more recently, by solvent evaporation.

(ii) The use of dry emulsions as a solid dosage form has gained much importance due to elimination of some drawbacks associated with liquid emulsions, such as physical instability, relatively large volume of administration as compared to solid dosage forms, strict storage conditions (e.g. refrigeration required), dosage precision problem, possible patient incompliance, and difficulty in sterilization.

Self-emulsifying drug delivery systems (SEDDS)

(i) These are physically stable, isotropic mixtures of oil, surfactant/ emulsifier (and co-solvent) and drug, which forms fine o/w emulsions on exposure to an aqueous medium.

(ii) It offers several advantages in comparison with lipid solutions, such as increased drug loading capacity, increased rate and extent of absorption as well as improved reproducibility in the bioavailability.

a. The hydrophile-lipophile balance (HLB) system is a measure of the overall hydrophilicity/ hydrophobicity of a surfactant or emulsifier; compounds with HLB < 12 is considered lipophilic, whereas those with HLB > 12 is regarded hydrophilic
b. The loss of solvent capacity is likely to increase the risk of drug precipitation during dispersion in an aqueous medium

(iii) Additionally, the formation of small droplets may promote rapid stomach emptying and wide dispersion throughout the GI lumen, thereby minimising local exposure of the GI mucosa to surfactants at high concentrations and reducing the irritation.

The role of silica-based materials in oral delivery of poorly water soluble drugs

1. A few mechanisms have been proposed through which silica-based materials improve the oral bioavailability of poorly water-soluble drugs:

(i) preservation of drug molecules in the amorphous or molecularly dispersed form and increased drug wettability in aqueous media, which lead to enhanced dissolution or release kinetics[25].

(ii) solubilisation of drugs at a supersaturation state in the GI fluids, which creates a driving force which favours drug absorption across the intestinal membrane.

(iii) Silica-based drug delivery systems can be categorised into three types:

(A) mesoporous silica xerogels.
(B) ordered mesoporous silica-based materials.
(C) mesoporous hollow silica spheres.

(a) Silica-based xerogels are amorphous, porous materials in which the

drug molecules are encapsulated inside the silica matrix using sol-gel technology. This has been investigated for some poorly water-soluble drugs such as cisplatin, nifedipine and ibuprofen.

(b) Ordered mesoporous silica based materials shows more well-defined surface properties, and their porous interiors are well suitable for encapsulating different molecules of drugs such as itraconazole, fenofibrate and carbamazepine[27], in which the encapsulated drug molecules are released mainly via a diffusion-controlled mechanism.

(c) Mesoporous hollow silica spheres facilitates a higher drug loading capacity through the hollow core structure. E.g., ibuprofen.

Some clinical studies conducted by have demonstrated an enhanced bioavailability effect for a poorly water-soluble antibiotic, amoxicillin trihydrate, resulting from a tablet formulation containing fat-silica matrix; enhancement effect was found to increase with higher silica content in the tablet formulation.

The synergistic role of lipid and silica excipients enhanced the oral absorption of poorly water-soluble drugs.

CONCLUSION

It can be concluded that a novel silica-lipid hybrid microparticulate system is used for enhancing the oral absorption of low solubility and low permeability of (BCS Class IV) drugs. It describes the systematic *in vitro* characterization of dissolution and lipolysis properties. Silica-lipid hybrid microparticles include the drug solubilising effect of dispersed lipids and stabilizing effect of hydrophilic silica particles to increase drug solubilisation, which leads to enhanced oral bioavailability.

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Table 1.1A BCS Classification

Class I High solubility, High permeability E.g. verapamil, acyclovir, propranolol	Class II Low solubility, High permeability E.g. cyclosporin, ketoprofen, mebendazole
Class III High solubility, Low permeability E.g. ranitidine, frusemide, acyclovir	Class IV Low solubility, Low permeability E.g. ciprofloxacin, mebendazole, frusemide

Table 1.1B Biopharmaceutics Drug Disposition Classification System (BDDCS)

Class I High solubility, Extensive metabolism E.g. verapamil, propranolol	Class II Low solubility, Extensive metabolism E.g. cyclosporine, ketoprofen, mebendazole
Class III High solubility, Poor metabolism E.g. ranitidine, acyclovir	Class IV Low solubility, Poor metabolism E.g. ciprofloxacin, frusemide

Table 1.1 Biopharmaceutical classifications of drug substances
(A) FDA Biopharmaceutics Classification Scheme (BCS)
(B) Biopharmaceutics Drug Disposition Classification System (BDDCS)[1]

Table 1.2 Comparison of various formulation technologies for poorly water-soluble drugs[9]

Technology	Potential advantages	Potential disadvantages
Physical modifications		
Micronisation (conventional)	Known technology; freedom to operate; easily adaptable to pharmaceutical manufacturing set-ups; relatively inexpensive and reproducible production; solid dosage form	Insufficient improvement in dissolution rate; no effect on the saturation solubility of drugs (these limitations also apply to other micronisation techniques)
Dense gas technology	Alternative nanocrystal processing method.	Unproven technology for industrial use; secondary process required to avoid aggregation of nanocrystals
Fluid pearl- or ball-milling	Established products on the market; experienced technology provider (Elan Corporation); versatility to produce solid or liquid dosage forms	Available only under license; secondary process required to avoid aggregation of nanocrystals
Crystal habit Modification	Relatively inexpensive; versatility to produce solid or liquid dosage forms	Risk of polymorph instability; possible need of incorporating stabilisers to inhibit crystal growth/ change
Surfactant and cosolvent system	Relatively high solvent capacity for hydrophobic compounds	Possible poor tolerance to excipient-related side effects in chronic use; tendency of drug precipitation on excessive dilution
Supersaturating drug delivery systems (solid solutions/ dispersions)	Freedom to operate; new melt extrusion technology offers solvent-free continuous process operating at a lower temperature; direct filling of semi-solid materials into hard gelatin capsules	Unpredictable physical stability of drug/ polymer in the product; limited scale-up of the manufacturing processes; requirement of a surfactant- or amphiphilic polymer-based additive to assist complete dissolution or to maintain supersaturation state
Lipid-based formulations	Versatility to produce solid or liquid dosage forms; potential in reducing food effect on bioavailability	Limited to highly lipophilic drugs; not feasible for formulating into conventional compressed tablets due to insufficient physical integrity and mechanical strength
Cyclodextrins (CDs)	Versatility to produce solid or liquid dosage forms; may offer protection to acid-labile drugs in the GI tract	May reduce drug permeability depending on the drugs' affinity for carrier or membrane; potential toxicity associated with less hydrophilic CDs
Chemical modifications		
Pro drugs	Better physical and chemical stability during storage compared to amorphous formulations; a potential way of reducing GI toxicity and presystemic metabolism	Can be a time-consuming and costly process
Salt formation	Better physical and chemical stability during storage compared to amorphous formulations	Not feasible for neutral and very weakly acidic/ basic compounds; potential reconversion into aggregates of the original poorly soluble acid/ base forms when dispersed in GI

Table 1.3 Currently marketed lipid excipients include[15]

Class of lipid excipients	Examples of excipients used in marketed lipid based oral products	Solubilizer	Emulsifier	surfactant	Others
Fatty acids	Oleic acid, soya fatty acids	Yes	No	No	No
Natural oils and fats	Medium Chain Triglycerides: Coconut oil, palm seed oil	Yes	No	No	No
	Long Chain Triglycerides: Olive oil, soya bean oil	Yes	No	No	No
Semi synthetic MG,DG,TG	Medium chain glyceryl mono & dicaprylate	Yes	No	Yes	Co-emulsifier
	MCT Glyceryl tricaprylate/caprate (miglyol 810)	Yes	No	No	Vehicle for capsule formulation
	Long chain MG Glyceryl mono oleate (capmul GMO)	Yes	No	Yes	Wetting agent, vehicle for capsule formulation
Semi-synthetic PEG derivatives of glycerides and fatty acid	Medium chain glycerides	Yes	Yes	No	Vehicle
	Long chain glycerides	Yes	No	No	Vehicle for soft gels, co-emulsifier, cosurfactant
	PEG 1500 Glyceryl laurate (Gelucire 44/14)	Yes	No	Yes	Semi-solid matrix. Capsule vehicle.
Cholesterol and fatty lipids	Egg lecithin, soyabean lecithin	Yes	Yes	Yes	(in mixed micelles, emulsions, liposomes)
Polyglycerol fatty acid esters	Polyglycerol-3-dioleate (plurol oleique CC 497)	Yes	Yes	Yes	Vehicle for capsule
	Polyglycerol-10-decaoleate (caprol 10 G100)	Yes	Yes	Yes	lubricant, crystallization inhibitor.

Table 1.4 Lipid classification based on their interactions with water[15,19]

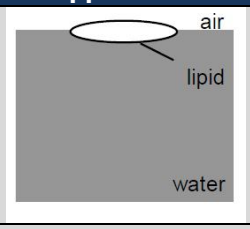
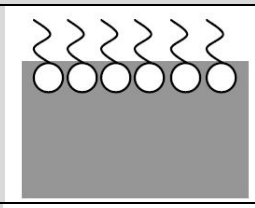
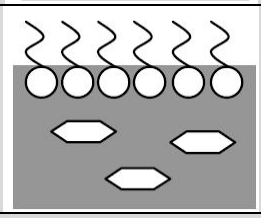
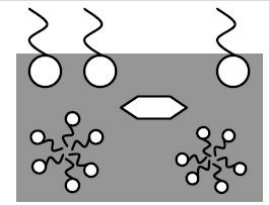
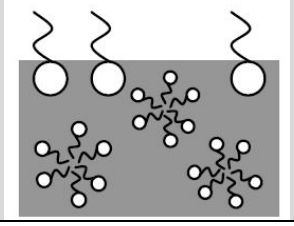
Class of lipids	Physical appearance	Schematic physical appearance	Examples
Non-polar lipids	Surface: will not spread to form a monolayer Bulk: insoluble		Cholesteryl esters, paraffin oil, carotene, hydrocarbons
Polar lipids			
I (Non-swelling)	Surface: Stable monolayer Bulk: insoluble		TG, DG, cholesterol, fat soluble vitamins (A,D,E,K), long chain FA
II (Swelling)	Surface: stable monolayer Bulk: insoluble		MG, phospholipids
IIIA (Swelling amphiphiles with lyotrophic mesomorphism)	Surface: unstable monolayer Bulk: liquid crystalline intermediates Micelles		Detergents, sodium and potassium salts of long chain FA
IIIB (Swelling amphiphiles without lyotrophic mesomorphism)	Surface: unstable monolayer Bulk: micelles		Bile salts, saponins

Table 1.5 Comparison of the properties of gastric lipase and pancreatic lipase

Properties	Gastric lipase	Pancreatic lipase
Origin	Gastric mucosa	Pancreas
Maximum catalytic pH	3.0 - 6.0	6.5 – 9.0
Measured medium pH	1.5 - 4.0	4.0 – 6.8
% TG Hydrolysis	10 – 20% (in stomach) 10 % (in small intestine)	60 – 90% (in small intestine)
Typical reactions	TG =DG+FA	TG =DG+FA DG=2-MG+FA 2-MG=1-MG=Glycerol+FA
Cofactor	NIL	Colipase

Table 1.6 Lipid formulation classification system (LFCS) based on the types and compositions of lipid and surfactant excipients as proposed by Pouton

Formulation type, properties	Type I	Type II	Type IIIA	Type IIIB	Type IV
Description	Simple lipid solution or suspension	SEDDS	SEDDS/SMEDDS	SMEDDS	Surfactant/ cosolvent blend
Typical compositions					
TG/mixed glycerides	100%	40-80%	40-80%	< 20%	--
Hydrophilic cosolvents	--	--	0-40%	50-100%	0-50%
Surfactants	--	20-60% HLB <12	20-40% HLB >12	20-50% HLB >12	0-20% HLB <12 30-8-% HLB >12
Particle size of dispersion	Coarse	100-250 nm	100-250 nm	50-100 nm	<100 nm
Significance of aqueous dispersion	Limited importance	Solvent capacity unaffected	Some loss of solvent capacity	Significant phase changes and potential loss of solvent capacity	Loss of solvent capacity
Significance of digestability	Crucial requirement	Not crucial but likely to occur	Not crucial but may be inhibited	Not required and not likely to occur	Not required and not likely to occur

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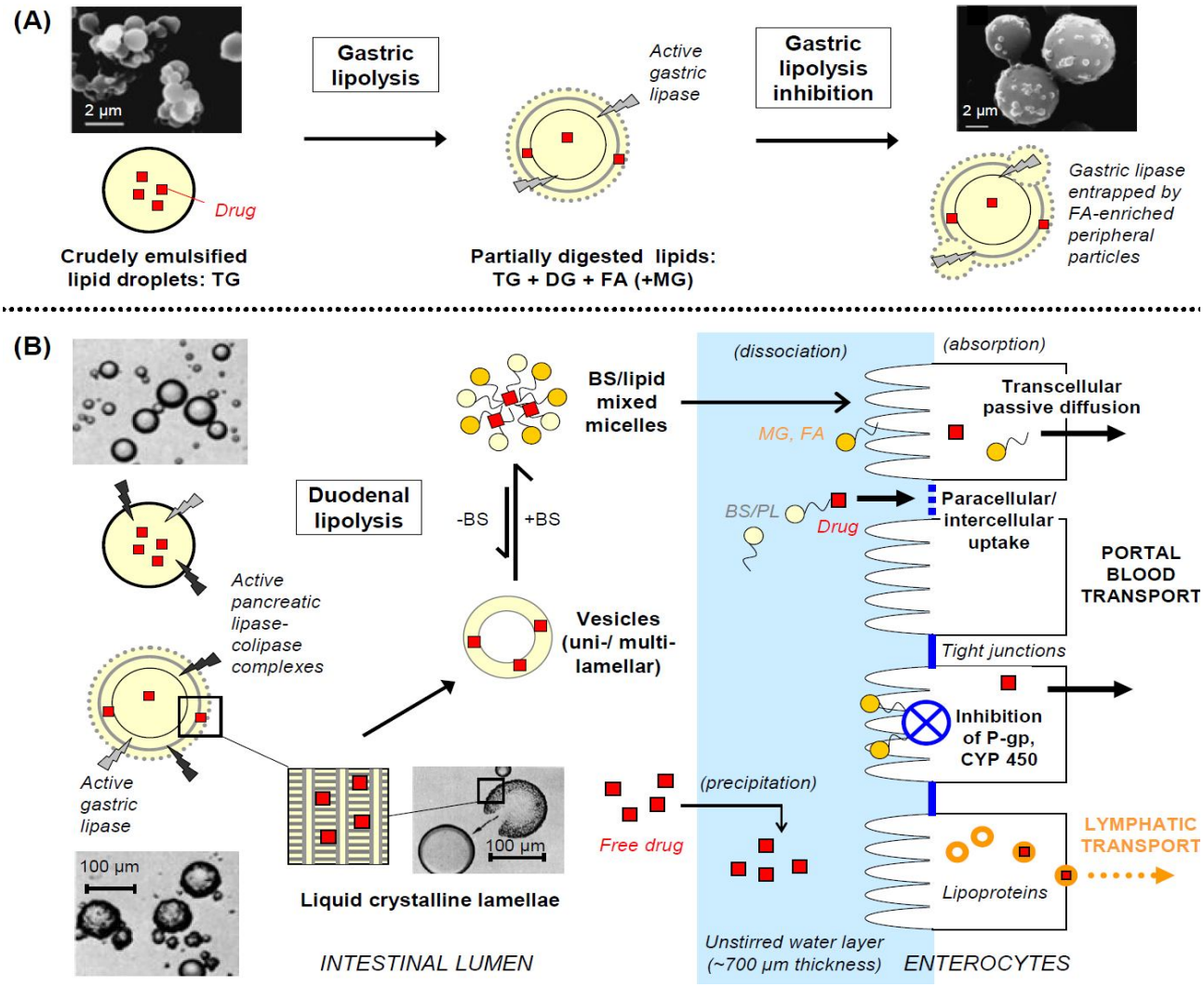

Figure 1. Schematic diagram illustrating the gastrointestinal digestion of triglyceride substrates and fate of the encapsulated drug molecules