LIPID BASED DRUG DELIVERY SYSTEM: CLASSIFICATION, DRUG TRANSPORT ACROSS ENTEROCYTE, ROLE OF LIPID CHAIN LENGTH IN SUPPRESSION OF BODY FAT ACCUMULATION

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ABSTRACT

The major challenge in the oral delivery of dosage form is poor absorption mainly due to the deficit aqueous solubility of drug that may lead to erratic bioavailability and hence therapeutic failure. It has been reported that about 40% of new chemical entities (NCEs) being short of aqueous solubility cannot be formulated conventionally. Every efforts made by the formulators to step-up the solubility and bioavailability of these entities. For this oral lipid based drug delivery system are attracting considerable attention due to their capacity to step-up the solubility, dissolution, facilitating gastrointestinal absorption and eliminate the effect of food on the absorption of poorly aqueous soluble or lipophilic drug and thereby increasing the bioavailability. Over the decades several strategies are being designed in lipid based drug delivery system had justified the remarkable improvement in bioavailability. This review highlighted the brief description of lipid absorption and transport across the enterocytes, drug candidate selection, potential screening of excipient intended for lipid based drug delivery, role of long, short and medium chain triglycerides in suppression of body fat accumulation, and Pouton's classification for lipid based drug delivery system.

Key words: SEDDS, Bioavailability, Medium and long chain triacyl glycerol (MLCT), *In vitro* digestion, Solid carrier, SNEDDS.

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INTRODUCTION

Oral route is one of most commonly used route for drug administration. This route remains most popular since ancient time due to easy administration. In order to achieve the appropriate therapeutic value for the vast number of drug which are present in nature as well synthesized because of their poor aqueous solubility formulators face obstacles. It has been reported in the literature that about to 40% or more of new drug candidates available possess poor aqueous solubility and hence not suitable for oral delivery owing to the low bioavailability, subject variability, proportion of dose to be incorporated in the formulation [1,2]. For this instance lipid based drug delivery system has been designed to accelerate the solubility, bioavailability of poorly aqueous soluble substances. Various approaches are being made in the last decade using lipid carrier but among these self emulsifying (microemulsifying/nanoemulsifying) is most recent interest of topic needs valuable attention by the formulators and had been proved fruitful results in nanosizing the drug molecule. The self microemulsifying or nanoemulsifying drug delivery system is comprised of transparent, clear mixture of oils, surfactants, cosurfactants and solvents. The surfactants having higher HLB value are

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usually selected along with cosurfactant with moderate HLB value [3]. The extent of drug absorption from such a formulation into systemic circulation depends upon the liberation of drug from lipidic vehicle on self dispersibility or self spontaneity. This technology has dramatically changed the attention of scientist to think more over nanoscale technology and explore the effort in creating significance drug therapeutics. Drug delivery based on nanoscale/lipid carrier is helpful in reducing hydrophobicity, improving compatibility with GI fluid, promoting dissolution, reducing drug precipitation, improving biodistribution, drug disposition, minimizing drug degradation in the intestinal milieu, and achieving the site oriented targeting [4,5]. Lipid-based drug delivery systems (LBDDS) enhances the bioavailability of highly lipophilic compounds because drug in such a system remain in the dissolved state until it is absorbed, thus overcoming the barrier of slow dissolution rates [6]. When this is administered orally presence of food may be the factor that could be taken consideration in hindering or enhancing the drug absorption. Willmann et al. addressed thatmultiple factors in the GI tract interplay a significant role in drug solubilization fed or fasted state, content of foods and therefore the unpredictability in absorption of poorly soluble drug are resulted [7]. Lipid based formulations eliminate the pre-absorption variability on the GI tract and help in improving the bioavailability of those drug showing low therapeutic index [8]. Despite counter acting the pre-absorption variability, eliminating dissolution steps this formulation also promised drug absorption via P-glycoprotien mediated drug efflux [9], membrane-bound cytochrome enzymes [10], lymphatic transport into biological systems that overcomes first pass metabolism and increasing membrane permeability. The processing procedure for lipid based system often cost at beginning but has conspicuous advantage over conventional solid dosage form e.g., once the product has been encapsulated in the HPMC capsule shell need not required other tedious process like coating to address the product elegancy, taste-masking property, searching for stable crystalline form of drug, maintaining dust-free, clean up area (for potent drugs) and thus eliminating the additional operation. This review briefly focused on fate of lipid in GI tract, potential selection of excipients, innovative technology explored for drug delivery [11].

Anatomy and fate of lipid (digestion, absorption and bioavailability) in human body

In the very beginning of 1842 Gruby and Delafond reported their observations on the absorption of ingested fat from intestinal villi to the intestinal lumen in the Academy of Sciences in Paris. Gruby and Delafond explained the intestinal epithelial cells of fat-fed animals as crammed with small particles and globules of fat. The coarsely emulsified fat in the intestinal lumen passed directly into the open epithelial cells, which got converted into a homogeneous and smooth emulsion of small particles and then transferred to the central lacteal [12]. The nutritional supply of dietary lipid contains mainly triglycerides or neutral fat, comprised of fatty acids. The food containing phospholipids, cholesterol and fat soluble vitamin are sloughed by epithelial cells of intestine and dumped into bile contents considerably.

The intraluminal processing of lipid significantly affect the solubilization, absorption and bioavailability of lipid containing drug. A normal adult diet constitutes 60-80 g of fat and some of the part is from endogenous origin which together constitutes the 100-140g/everyday. Whereas, a western diet has 90 to 100 g of fat per day [13]. So it has become important to address the fate of lipid absorption. Processing of food laden fat or formulation-derived lipids generally begins in the stomach where triglycerides (TG) are hydrolysed to diglycerides (DG) and fatty acids (FA) by the acid-resistance lipases i.e., lingual lipase and gastric lipase. Gastric lipase, has an optimum pH range of 3-6 are secreted by the gastric mucosal layer and cleaved the ester bonds [14,15]. Salivary glands resides in sublingual cavity secretes lingual lipase, having an optimum pH of 4 preferentially hydrolyses TG but the cleavage point for that lipase antagonistic to prior one [16,17]. Some other lipase more prone to get cleaved the medium chain triglycerides (MCT) compared with long chain triglycerides (LCT) are acidic in nature and do not hydrolyse phospholipids or cholesterol esters [13]. Digestion via acid lipases accounts for only approximately 10 to 30% of the overall hydrolysis of ingested TG in food and mostly important to animals (rats and mice), whereas in humans, rabbits and guinea pigs gastric lipase predominates [18]. The stomach is the primary site of initial lipid emulsification in the GI tract and the process is being facilitated by a combination of gastric agitation and gastric emptying. The lipophilic drug molecules are mostly solubilized from upper part of G tract, pancreatic and biliary secretion (salts, phopholipid and cholesterol ester) enhance the process of solubilization and absorption of these molecules usually occurs in the small intestine owing to large surface area [19]. The residence time of a lipid molecule in the upper GI tract is limited and transit time in the small intestine is 3.5-4.5 h in healthy volunteers, nonetheless fat can extend the short intestinal transit time up to 1 h [20]. Yet this affect is not thought to be significant in drug delivery. The short transit time is the obstacle in the pathway of absorption of lipid molecules and before they are expected to reach the colon and bioavailability is considerably reduced [21].

The mixed bile salt, phospholipid contents of lipid digestion products contained in a mixed bile salt, micellar phase first need to be dissociated in order to be absorbed into the enterocyte. As we know that intestinal tract is richly supplied with both blood and lymph because the structure lamina propia that present around the enterocytes

are highly vascular lies in close proximity with blood and lymphatic vessels [22].

Lipid and drug transporter across the enterocyte

As we know that the large molecules of triglycerides/lipid droplets are not transported into the cell because of hydrophobic in nature. Therefore it is required to breakdown the triglycerides into smaller one such as monoglycerides, fatty acids of hydrophilic characteristics for easy absorption. Bile salts, gastric lipase and pancreatic play an important role in the digestion of triglycerides. Large triglycerides lipid droplets in presence of bile salts, pancreatic lipase changes into fatty acids and monoglycerides in the intestinal lumen. A series of water lamellae appear as unstirred water layer (UWL) present before the absorptive surface of brush border basement membrane (BBM) of enterocyte. These water lamellae act a rate limiting step in diffusion and permeation of hydrophobic drug but it is fast across the intestinal brush border area [23,24]. Inside these cell monoglycerides and fatty acids are transported to Endoplasmic reticulum (ER). The contents of ER (Golgi apparatus, triglycerides, lipoprotein and other lipids) packed with entering components (lipids) results in chylomicrons. Later on chylomicron are extruded from Golgi apparatus into exocytotic vesicles which are being transported to the basolateral part of enterocyte. Finally, chylomicron are oozing out via exocytosis after fused with cell membrane into the capillary blood, through which transported to lymphatic vessels that penetrate into microvilli. Now, the lymphatic vessels enriched with chylomicron are then drained to blood through lymphatic system [23,24].

From the enterocyte drug molecules followed two potential pathways for absorption in the blood. Through first pathway drugs likely to enter into blood capillaries and are transported to the portal blood and the other into the lymph capillaries. A high molecular weight drug more preferably follows the pathway of lymphatic vessel for absorption as it more permeable to the lymphatic capillaries. The former pathway is the commonly accepted mechanism for absorbed drugs are transported into portal blood with high rate (500-fold) as compared to that of intestinal lymph. Following absorption into the blood capillaries, chylomicron incorporated drug has to travel through the hepatic portal system, in the meanwhile they expose to metabolic enzyme and first pass metabolism is the major obstacle to the absorption of lipophilic drug. The lymphatic pathway of drug transport offers a number of advantages on contrary of blood capillaries on per oral absorption, firstly it is a liver bypass mechanism and thus avoid hepatic first-pass metabolism. Since it will increase oral bioavailability those drug molecules which are more prone to get metabolized in liver [25].

It has been found that protein lipid molecules in the basolateral membrane of enterocyte facilitate the absorption of endogenous lipids and lipids from exogenous

sources [26,27]. Some of these protein molecules had been identified as Niemann-Pick C1 Like1 (NPC1L1) [28,29] ATP-binding cassette (ABC) [30,31] P-glycoprotein (P-gp), ABCA1 [32], ABCG5 and ABCG8 [33] associated with enterocytic cells of intestine. Few lipid and drug transporters and their function are being reported to be actively involved in intestinal lymphatic transport are given in the Table 1. A recently identified P-glycoprotein (P-gp) acts as efflux pumps having broad specificity for a variety of substrates categorized under the ATP-binding cassettes (ABC) are greatly insisted in transport of lipids.

The cytochrome P-450 3A4 (CYP3A4) enzymes are located in the smooth endoplasmic reticulum of the enterocytes are major barrier to the absorption of lipophilic drugs, because most of the drug molecules undergo oxidative metabolism in the intestinal wall [34]. Multidrug-resistance associated proteins (MRPs) are another barrier was believed to be act through the elimination of compounds from the cell via efflux pump system [35].

Selection of drug candidate for lipid based drug delivery

The biopharmaceutics classification system (BCS) is a scientific platform or a drug development tool, which takes into account three major factors that govern the bioavailability (rate and extent of drug absorption) from immediate solid dosage form, dissolution, solubility, and intestinal permeability. According to Word Health organization (WHO) guidelines, BCS has classified the drug molecules listed on the essential medicinal list (EML) into four different classes (I, II, III and IV classes) based on their solubility and permeability parameter:
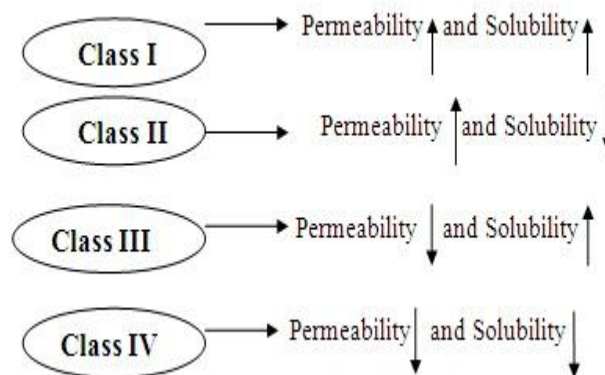
The solubility class boundary has been designed on the basis of highest dose strength (HDS) of a product has to dissolved in specified volume corresponding to a pH range. Drug substances are assumed to be highly soluble (HS), if the HDS is soluble in 250 ml or less aqueous media over pH range of 1.0 to 7.5. More than 250 ml of volume of media and over the same pH range is given for Low solubility (LW) drugs. In fact, the estimated volume of 250 ml is taken out from bioequivalence study protocol that recommends drug product administration to fasting

state human volunteers with a glass of water. This class boundary gives an account for the minimum fluid volume is required in stomach when the drug is administered during a conventional fasting bioequivalence study. Moreover, BCS class II and IV is more suitable drug candidate is often incorporated in lipid vehicle to combat the poor solubility [36]. From BCS classification we came to acknowledge the poor aqueous solubility or dissolution is the limiting factor which mandates to get partitioned into the chylomicron enriched with triglycerides and which is the preliminary thing needs to scrutinize before development of lipid based system. Chylomicron contents of lipid is overall determining factors that quantify the concentration of drug may be transported via intestinal lymphatics reported by Charman et al [37]. Partition coefficient, lipophilicity (e.g., octanol:water Log P), drug solubility in Generally regarded as safe (GRAS) approved excipients, and fatty meal effect on the administered dose is the preliminary indication for the potential selection of drug candidate [38,39]. The log p value or partition coefficient of drug significantly determined in order to know the lymphatic transport. The lipophilicity of drug can be calculated by determining the log p value. The highly lipophilic drug with log P value greater than 5 and solubility greater than 50 mg/ml would be significant for lymphatic transport system and improve oral bioavailability [37]. The log p value guided about the membrane permeability, passive diffusion and facilitated diffusion. The drug with high log p value is more soluble in Long Chain Triglycerides or Medium Chain Triglycerides while lower log p value is more soluble in monoglyceride esters [40].

Potential screening of excipients suitable for lipid based delivery

Identification of surfactant is essential for solubilizing aid of drug entity and spontaneously forming o/w emulsion required for nanoscale formulation. It is the backbone of self emulsifying formulation [11]. The surfactant can categorize on HLB scale discovered by Griffin. The value assigned to this is 1-18. The HLB value below 10 provides lipophilicity and above 10 is hydrophilicity. The surfactants can be scrutinized based on equilibrium solubility background for oral lipid based system. Generally, a blend of surfactants comprised of surfactants and cosurfactants are suitable for optimum solubilization. Xi et al. investigated the positive effect of cosurfactant (transcutol P) on the droplet size of the stable emulsion. An optimum concentration of cosurfactant is required to form the least droplet size of emulsion. This may be attributed to the fact that addition of cosurfactant along surfactant causes stabilized interfacial film to expand [41]. The cosurfactant hereby used to assist the further solubility of the system to obtain the stable self emulsifying preparation [4,42]. The HLB value in the blends of surfactant predicts the fate of stable naoemulsion.

The surfactants selected in such way that it should accommodate maximum quantity of drug component. For this either one or a blend of surfactants with high HLB (>10) and low HLB value (<10) taken to assure better solubilization capacity and uniform droplet distribution following self-emulsification [43]. It is classified into ionic, nonionic and ampholytics. Non ionic surfactant is highly desirable for SMEDDS (self microemulsifying drug delivery system)/ SNEDDS (Self nanoemulsifying drug delivery system) preparation due to narrow range of toxicity and provides good self emulsification [5,9]. Examples of nonionic surfactants extensively used such as polysorbates 80 (e.g., Tween80, and 20), Polyoxyl 35 castor oil (e.g., Cremophor EL), Medium chain glycerol and PEG esters (e.g., Labrasol), transcutol, peceol, gellucire 44/14 , Solutol HS 15, polymers (e.g., pluoronic P85), ethoxylated triglyceride (e.g., Cremophor RH40), D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS), Glycerol monooleate (e.g., Peceol®), lauroylmacrogol glycerides (Gelucire® 44/14) etc. Among the surfactants, polysorbates are available in variable HLB grade with good oral acceptability [44]. The nonionic surfactant can be classified into various categories based on the acyl chain length such as medium chain, long chain, short chain fatty acids or number of carbon present in fatty acid chain may be short-chain fatty acids (SCFA), medium-chain fatty acids (MCFA), and long-chain fatty acids (LCFA). Medium chain fatty acids are most frequently used because it is easily digested and absorbed. Unlike other fats, they put little strain on the digestive system and provide a quick source of energy. MCFAs are present in edible oil and food items are caproic acids, caprylic acid and capric acid. The primary sources of MCFAs are coconut oil (15%), palm kernel oil (7.9%), butter (6.8%), milk (6.9%), yogurt (6.6%) and cheese (7.3%) of total fatty acid [45]. Other sources of medium chain trigylcerides, Neobee M5, propylene glycol dicaprylate/dicaprate (Captex 200, captex 355) palm seed oil. The size of the fatty acid chain play significant role in better absorption and digestion as well as in healing properties of MCT in coconut oil are contrastingly different from the LCT. Owing to these outstanding properties of MCT unlikely, few food items contain appreciable amount of MCT. When compared LCT with MCTs in consumption, MCTs has found to raise energy expenditure (EE) in humans [5-10] and is frequently leads to lower body weight (BW) gain and fat depot size in growing animals [46].

Role of MCT in suppression of body fat accumulation

Obesity is a common disease in which body fat is excessively accumulated, is likely to be accompanied by many diseases such as diabetes, hyperlipidemia, and hypertension. Lavau and Hashim conducted an experiment in laboratory animals by feeding them LCT and MCT and concluded that MCT is less accumulated as body fat than LCT found in edible oil [47]. It is useful for the obesity

related problem. Takeuchi et al. performed a large-scale study on the body fat accumulation suppressing effect of MCT in humans by a double-blind study [48] in healthy subjects under strict dietary management. Selected 78-subjects were slightly fatter than the average (mean BMI=24.7) ate bread containing 14 g of the test oil daily as breakfast. More than 10,000 lunches and suppers were prepared given to the subjects for 12 weeks. Air displacement method were followed for tracing the body fat measurement, and found that in the subjects with a BMI of 23 or higher (slightly fat) the body weight loss was larger in the MCT ingestion group than in the common edible oil ingestion group [49].

Medium- and long-chain triacylglycerol (MLCT)

In addition to aforementioned property of MCT has some limitation like low smoking point (~ 140°C) foams are produced on deep frying, and indeed expensive. MLCT composed of fatty acids medium- and long-chain triacylglycerol and is prepared by mixing MCT and LCT and enzymatic trans-esterification. Table 2 displayed comparative study MCFAs with respect to LCFAs on absorption.

Role of MLCT in suppression of body fat accumulation

In the next context of the experiment put forwarded by Takeuchi et al. investigated the effect of MLCT on body fat accumulation-suppression in animal and human. MLCT diet containing feed was given for 6 weeks in rat and controlled group was treated with soybean oil containing feed it was measured the body fat deposition was smaller in that in rat contrasting to soybean oil diet control group [50]. Moreover, experiment was repeated in next year by incorporating a liquid diet containing 20 g of soybean or 5 MLCT oil per day for 3 weeks in healthy male volunteers in addition to usual diet, and the concentration of body fat deposition was monitored before and after the experiment. It was revealed that body fat amount increased in the soybean oil group, but remains unaltered in the MLCT group [51].

In another aspect of the invention a large-scale long-term nutrition study was performed similarly to the MCT evaluation study (as mentioned above) for body fat accumulation-suppressing effect of MLCTs. Diets of 82 healthy volunteers were strictly controlled under a double-blind condition for 12 weeks: only the vegetable oil contains MLCT bread was given daily as breakfast. Lunch and dinner and eating between the meals were carefully monitored finding led down large body weight loss in the MLCT group than in the LCT group (Fig. 1) [52].

The abdominal subcutaneous and visceral interrogation led to the body fat amount was reduced more in the MLCT group than in the LCT group [53,54]. Energy expenditure basis in healthy young women also unveiled that increased energy expenditure after MLCT ingestion contrast to soybean oil ingestion (Fig. 2) further confirmed that an MLCT-induced increased energy expenditure equally responsible for the suppression of body fat accumulation. In Japan, 2002, FOSHU (food for specified healthy use) approved the MLCT oil in controlling the body fat as less accumulated by virtue of safety established by Nosaka et al. in the same year, had been conducted in 10 healthy males and females by introducing 4-week ingestion study (42 g/day). No impairment in on liver or renal function was noted [55].

Classification of lipid based drug delivery system

Lipid based drug delivery system (LFCS) was compiled by Pouton in 2000 and later on 2006 updated components to differentiate more clearly the lipid formulations [6,56]. In the context of discussion, this system has been classified on the basis of probability of nanoemulsion formation upon dilution in the lacunae of intestinal fluid and followed by absorption and capability of overcoming the drug precipitation. The Lipid Formulation Classification System: characteristic features, advantages and disadvantages of the four essential types of 'lipid' formulations are given in Table 3. Type I systems formulation characterized by drug solution in triglycerides and/or mixed glycerides derived from vegetable or synthetic source. Drug precipitation are sole problem observe with this type of system which can be stabilized by adding low concentrations of emulsifiers such as 1% (w/v) polysorbate 60 and 1.2% (w/v) lecithin. These systems having limited or no solubility in water as it lacks surfactants and poorly dispersible in water. Such system do not easily dispersed themselves in the intestinal contents needs to incorporate bile salts, digestive enzymes, phospholipids to promote drug dispersion in the colloidal aqueous phase. Type I lipid formulations promotes the choice for formulators to work for potent drugs or poorly soluble compounds where drug solubility in oil is limited and need to reduce the incorporated dose [57]. Both medium chain and long chain FAs are used in this formulation are digested by lipase, bile salt and phospholipids. Long-chain FAs digestion products have better solubility in bile salt-lecithin but swollen mixed micelles formed by LCT digestion products provide better environment for solubility [58]. The components used in these formulations are conveniently administered via oral route, safe, effective and stable and are approved by GRAS.

Porter et al. experimented on halofantrine, a lipophilic drug on the solubility characteristics after *in vitro* digestion is primarily depends upon the fatty acid chain length and finally they came to revealed that differences in bioavailability of halofantrine is an account of MCT, LCT and SCT (short chain triglycerides) solutions [38,59]. *In vitro* lipid digestion is performed in the intestinal milieu to know what exactly happening to lipid based formulation and to simulate the condition of formulation *in vivo* study. The process is triggered with

oral administration of lipidic component undergone a series of enzymatic hydrolysis by lipases from stomach results in the formation of simpler glycerides and fatty acids in the stomach. The partially digested glycerides come across the peristaltic movement of stomach forms partially digested emulsion or crude emulsion [60]. These formed crude emulsion passes to the small intestine that stimulate the secretion of bile salt, phospholipids, pancreatic lipase. These agents surround the emulsion and produce more stabilized emulsion with reduced droplet size indicated the end of enzymatic hydrolysis [61]. Now the lipid digestion product complexes with endogenous BS and PL formed colloidal vesicles that augment the solubilization process by maintaining the incorporated poorly water soluble drug in the dissolved state and counteract the precipitation of drug let to be consider the principal mechanism of drug absorption in the GI tract from *in vitro* lipid digestion of formulation. *In vitro* lipid digestion is a dynamic process that presents a rank order of different types of triglycerides (long chain, medium chain and short chain) of the anticipated *in vivo* performance and predicting the suitable lipidic delivery system of high *in vivo* drug solubilization [25]. Generally, for maximum simulation of lipid digestion process in *in vivo* condition an experimental set up is required such as pH-titrator, autoburette, and pH electrode.

In brief, the set up work on the principle of maintenance of constant pH that mimics the *in vivo* condition; higher degree of simulation of *in vivo* lipolysis process; addition of titrant in such a quantity that can react with free fatty acids stochiometrically and quantify the extent of lipolysis process. The librated free fatty acid during this process can remove by complexing with calcium ion that hastens lipolysis process [62]. Upon completion of this process experimental medium is centrifuged and three layered fraction is obtained an aqueous fraction consists of monoglycerides, fatty acids, and bile salts; second fraction is lipid phase comprised of undigested triglyceride and diglycerides followed by a sediments having undissolved fatty acids [63]. The rate and extent of digestion of LCT, MCT and SCT can assessed by this process. The *in vitro* digestion product of LCTs appears in 3-phased; oil, aqueous and sediments while LCTs into 2-phases oil and sediments [63]. The colloidal species formed on digestion of MCTs includes simple and complexes micelles and vesicles rather vesicles and complex micelles on digestion of LCTs. The vesicular phase was found to be providing solubilization on MCTs digestion of highly lipophilic drug whereas, mixed micellar phase predominantly aid solubilization on digestion of LCTs [25]. Few examples of commercially developed soft gelatin capsules corresponding to the type I formulations are Prometrium®, progesterone contents in peanut oil, Restandol®, testosterone undecanoate content in oleic acid and Depakene®, valproic acid content in corn oil.

Type II formulations typically known as self emulsifying drug delivery systems (SEDDS). It consists of a mixture of lipids and lipophilic surfactants having HLB value-12 that self emulsify to form fine oil-in-water emulsions globules upon exposure of aqueous media in GI tract [64,65]. The least content of surfactants for self-emulsification in type II formulation approximately 25% (w/w). Even at higher concentration of surfactant (50 % w/w) formulations can be optimized depending on the materials selection, viscosity of formulation is critical for the progress of emulsification in short time [64-66]. SEDDS conveniently encapsulated in hard or soft gelatin capsules to produce single unit dosage forms. Shortcoming of Type I formulation is improper and slow digestion, low dissolution rate are mitigated that are frequently observed with solid dosage forms, large interfacial area exist between the oil droplets and water phase permits efficient partitioning of drug for absorption [67]. Khan and Nazzal developed a eutectic-based self-nanoemulsifying drug delivery system (SNEDDS) of powder incorporated solid dosage form in US patent 2010/0166873 were comprised of cremophor (polyoxyl 35 castor oil), campule (medium chain mono- and diglycerides), essential oil, a copolymer of vinylpyrrolidone and vinyl acetate (Kollidon VA 64), maltodextrin, and microcrystalline cellulose and ubiquinone CoQ_{10} as a poorly water soluble drug with improve emulsification and dissolution [68]. Other example of SEDD of poorly water soluble drug CoQ10 compared with powder formulation issued to Balakrishnan et al [69] with improved solubility and bioavailability were composed of oil (Labrafil M 1944 and Labrafil M 2225), surfactant (Labrasol) and cosurfactant (Lauroglycol FCC and Capryol 90). The solubility of CoQ10 was determined in various oils, surfactants and cosurfactants with constant concentration of drug in all the formulations. Moreover, the particle size of emulsion, zeta potential and drug release profile was determined. The optimized SEDDS formulation consist of 65% (v/v) Labrasol, 25% (v/v) Labrafil M 1944 CS and 10% (v/v) Capryol 90 of each excipient showed minimum mean droplet size (about 240 nm) and optimal drug release profile in water. The *in vivo* study in rats of optimized formulation was compared to simple powder formulation reported that significant increase in the C_{max} and area under the curve (AUC) of CoQ10 concluded that self microemulsifying drug delivery system could be an effective for improving oral bioavailability of CoQ10. Shah et al. compared the bioavailability of SEDDS contained RO-15-0778, with a capsule of 55% wet-milled spray-dried powder and a tablet of micronized drug after administration of a formulation consisted of peanut oil and polyglycolysed glycerides as emulsifiers, a PEG 400 solution to dogs. *In vivo* study unveils that SEDDS formulation showed superior, with at least 3-fold higher C_{max} and AUC compared with the other dosage forms. Rapid release profile of the drug and increased solubilisation of drug in the gastrointestinal

lumen under normal peristalsis were in accordance with the improved drug bioavailability [70].

Type III lipid-based formulations, are characterized by incorporated hydrophilic surfactant (HLB value>12) cosolvents ethanol, propylene glycol, low molecular weight such as PEG 400 are categories as SEDDS or SMEDDS, SNEDDS depending upon the observed particle size of the formulation. Type III formulations can be further subdivided into Type IIIA and Type IIIB based on the criteria of hydrophilic component contents. Indeed, the identification mark of Type IIIA and Type IIIB system are greatly varying as observed visually. The potential risk of drug crystallinity with Type IIIB owing to the lesser lipid contents and higher amount of cosolvent although it forms clear dispersion with aqueous phase. Increased amount of cosolvent having additional advantage of improving solvent retention in the formulation so that greater quantity of drug can be dissolve and it would be easily accommodated in the formulation. But drawback of using cosolvent along with solvent is formulation losses solvent retention capacity and phase separation occurs may lead to partial drug precipitation. Before undertaking any such preparation formulators should be aware of such factors which often hinder formulating path[6,57].

Type IV lipid formulation are characterized by presence of pure surfactants or mixtures of surfactants and co-solvents. In general, drug precipitation is the common problem of poorly water-soluble drug in cosolvent. The drug precipitation in amorphous or crystalline form could be the advantage of only that obtained as the micronized form of suspension which can heal a bit of shortcoming of this strategy. In this regard the only path of overcoming the precipitation problem in the spectrum of formulation of poorly water soluble drug optimizing the structure of surfactant so as to make the surfactant hydrophilic since, loss of solvent capacity is less significant [71]. There are two problems that are to be considered before formulation using pure surfactants. The first is that formation of viscous liquid crystalline (or gel crystalline) phases at the surfactant-water interface. Therefore, surfactants usually take a considerable time to dissolve the drug in aqueous phase. The second is in this context is poor tolerance of the gastrointestinal tract due to irritant nature of pure surfactants are the concern. The adhesion of a partially dissolved viscous mass having copious amount of surfactant to the mucosal layer of the stomach or intestine would result in considerable local tissue damage and thus, microscopic bleeding are the risk factor. The blending of water-soluble surfactants with cosolvents improves the dispersion of surfactant and reduces the loss of solvent capacity. In the sense of present discussion, an example of type IV formulation is the amprenavir capsule formulation (Agenerase, GSK) is a, blend of tocopheryl PEG 1000 succinate (TPGS), PEG 400 and propylene glycol. TPGS is unlikely used surfactant in this formulation that evolved as a water dispersible form of vitamin E. Yu and coworkers explored the merits of TPGS by suggesting that inhibition of the ABC transporter P-glycoprotein may be a factor in bioavailability enhancement [72].

Table 1. Lipid and drug transporters along with their function in intestinal lymphatic transport [34]

Transporters (Lipid and drug)	Function
NPC1L1 (proteinous in nature)	Lipid transporter
P-glycoprotein	Intestinal lipid formation, absorption and intracellular trafficking of cholesterol
ABCA1	Facilitate absorption of cholesterol, enhance the formation of high density lipoprotein
ABCG5 and ABCG8	Reduce excess of intestinal and sterol absorption by facilitating efflux from interocyte
MRPs	Elimination of drug and compounds from the cell via efflux system resistance to cytotoxic drug such as vincristine and peptides, heavy metal anions as well as endogenous metabolites such as bilirubin glucuronides.

Table 2. Comparative study of MCFAs with LCFAs on absorption

MCFAs	LCFAs
Contrast to long-chain triacylglycerol (LCTs), MCTs is easily digested and absorbed.	Not easily digested and absorbed.
MCTs is completely hydrolyzed to fatty acids and glycerol by pancreatic lipase, and rapidly absorbed, even in disease condition where pancreatic secretion is reduced.	LCTs is hydrolyzed to 2-monoacylglycerol by pancreatic lipase, which further requires micelles to dissolve and then absorb in the mucosa of small intestine.
MCFAs are not readily re-synthesized to triacylglycerol. They are readily bound with albumin protein and transferred into portal blood,to the liver, where MCFAs departs from albumin fraction and are transported to mitochondria and where get oxidized rapidly.	LCFAs absorbed from the small intestine are resynthesized to triacylglycerol in small intestinal mucosa cells, form chylomicrons, released into the circulation via lymph vessels, and transported to the peripheral tissues (adipose tissue and muscle).

Table 3. The Lipid Formulation Classification System: characteristic features, advantages and disadvantages of the four essential types of 'lipid' formulations [56]

Formulation type	Materials	Characteristics	Advantages	Disadvantages
Type I	Oils without surfactants (e.g. tri-, di-and monoglycerides)	Non-dispersing, requires digestion	GRAS status; simple; excellent capsule compatibility	Formulation has poor solvent capacity unless drug is highly lipophilic
Type II	Oils and water- insoluble surfactants	SEDDS formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particle size 0.25–2 µm)
Type III	Oils, surfactants, cosolvents (both water-insoluble and water-soluble excipients)	with water-soluble components	drug absorption without digestion	on dispersion; less easily digested
Type IV	Water-soluble surfactants and cosolvents (no oils)	Formulation disperses typically to form a micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity on dispersion; may not be digestible

Figure 1. Medium-and long-chain triacylglycerol (MLCT)-induced changes in body weight and body fat amount in humans). Eighty-two healthy subjects were given bread containing MLCT or long-chain triacylglycerol (LCT) for 12 weeks as breakfast under controlled monitoring of diet. The values are presented as the means ± SE ($p<0.05$) [52].
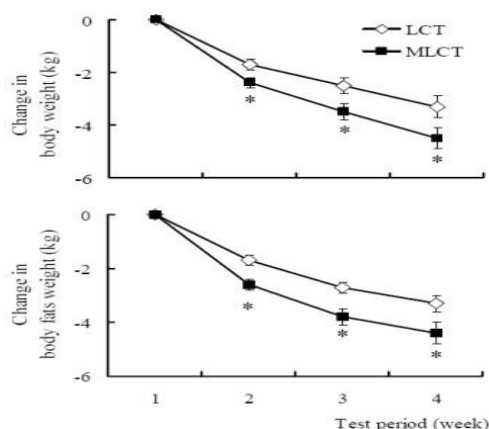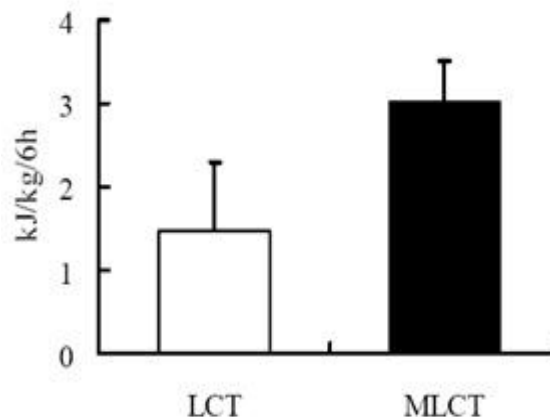

Figure 2. Depiction of energy expenditure and their measurement corresponding to LCT or MLCT ingestion in 15- healthy females for 6 hours. The values are presented as the means ± SE ($p<0.01$) [53,54].

CONCLUSION

Lipid based drug delivery system is novel approach to enhance the oral bioavailability of poorly soluble drug. As per the estimates more than 40 % of new drug entity suffers poor aqueous solubility because of biological barrier of membrane that leads to erratic bioavailability. The cytochrome P-450 3A4, multidrug-resistance associated proteins are biological that resisted the entry of digested fat into the cells. Other hand many lipid transporter insisted in the path of lipid transport to blood capillaries. The BCS class II and class IV drug mostly faces the poor solubility in the GI tract. The screening of excipient for enhancing the solubility of such class of drug is very critically considered that imparted better formulation modalities. The selection of appropriate chain length of lipidic excipient need to address that important role in suppression of body fat accumulation. Pouton classified lipid based drug delivery system into various classes. The reported type I formulations includes progesterone contents in peanut oil (Prometrium®), testosterone undecanoate content in oleic acid (Restandol®), and valproic acid content in corn oil (Depakene®). The Type I system need to explore more things because drug precipitation is sole problem associated with this. Type II systems said to self emulsifying system and many satisfactory works has been reported. In type III and IV system of formulation nanoscale of drug in molecularly dissolved form could be achieved depending upon the selection of excipient, self emulsifying domain and phase separation.

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