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LIPID BASED DRUG DELIVERY SYSTEM FOR ENHANCING ORAL BIOAVAILABILITY – A CONTEMPORARY REVIEW

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ABSTRACT

Lipid based formulations such as self emulsifying drug delivery system (SEDDS) and self microemulsifying drug delivery systems (SMEDDS) are designed to improve the oral bioavailability of BCS class II and IV drugs. This review emphasizes on various types of excipients to be selected and used in SMEDDS formulations with their significance and criteria for their selection. Solubility is a key determinant in the selection of excipients. The excipients used in above formulations influence the absorption of drugs and thereby facilitate the bioavailability of poorly water soluble drugs. Composition of lipid based formulations includes oils, surfactants, co-surfactants, solvents and co-solvents, which improve the oral absorption of highly lipophilic drug compounds. Solubilization of drug in lipid excipients leads enhanced absorption that results in improved oral bioavailability. Lipid based drug delivery system improves the absorption by inhibiting p-glycoprotein and enhancing drug transport to the systemic circulation through intestinal lymphatic system. Factors affecting the bioavailability of the drug from lipid based drug delivery system include digestion of lipid, lipophilicity of drug, mean droplet diameter. Lipid excipient increases the oral absorption by retarding the gastric emptying. Various marketed formulations are discussed in this review. Lipid based drug delivery system delivers the proteins and peptide by solid lipid nanoparticles, liposomes, these are potential for enhancing oral delivery.

Keywords: Lipid based dosage form, oral bioavailability, lymphatic transport, surfactants, and lipids.

INTRODUCTION

Oral route is the most prominent route for drug therapy with water soluble drugs[1]. Whereas water insoluble drugs with poor oral bioavailability are interested drug candidates for formulation technology and research is been focused on design of lipid based formulations. Lipids are the carriers for the delivery of poor water soluble drugs[2]. Various lipid based formulations such as self emulsifying drug delivery system (SEDDS) and self micro emulsifying drug delivery systems (SMEDDS) have been attempted for enhancing absorption and bioavailability[3]. As an outcome of continuous research on lipid based formulation, it was understood that the lipid vehicles play an important role in the design and lead to the success of drug delivery by controlling the drugs' absorption rate based on their digestibility. Oily solutions, oil suspensions, emulsions (coarse and micro), self-micro or self-nano emulsifying drug delivery systems (SMEDDS/SNEDDS) are considered as lipid based formulations. The SMEDDS are thermodynamically stable and optically transparent preparations. They are critically composed with oil, surfactant and co-surfactant/co-solvents. As there are multiple excipients used in design and development of microemulsions, the relative solubility and affinity of the drug for each component is required to assess their suitability in the development of SEDDS/SMEDDS. These excipients have the ability of forming fine oil in water microemulsion with droplet size of submicron range. These formulatory excipients are also known as permeability enhancers[4]. These excipients can also inhibit both presystemic metabolism and intestinal efflux mediated by P- glycoprotein (P-GP) resulting an increase in the oral absorption of cytotoxic drugs[5, 6].

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Factors to be considered in designing of lipid based formulations:

Capacity of the solvent, properties of lipid excipients, lipophilicity of surfactants, excipient digestion in GIT and solvent miscibility are to be considered in the design of microemulsions.

Lipid-Based Dosage Formulations-outputs:

Liquid lipid formulations are manufactured either as soft or hard gelatin capsules, whereas semisolid or solid formulations are filled into hard gelatin capsules.

Commercially available oral lipid-dosage forms are either filled in capsules or represent bulk oral solutions. Soft and hard gelatin capsules are used for lipid-based formulations. Lipid based formulations were successfully applied to several commercial products includes Sandimmune® and Neoral® (Cyclosporin A), Fortovase® (Saquinavir) and Norvir® (Ritonavir) [7, 8]. Cyclosporin A (CsA) is a potent immunosuppressive drug, used in organ transplantation; it is a cyclic undecapeptide having poor aqueous solubility[9]. Several formulations were developed to improve the solubility and bioavailability of cyclosporine A, which eventually led to discovery of Sandimmune® as undigested lipid phase. Sandimmune Neoral® showed better performance than Sandimmune® because micellar phase formation due to predigestion of oily phase[10]. Studies were evident that positively charged self emulsifying drug delivery system (SEDDS) showed higher blood levels for CsA compared to that of negatively charged SEDDS[11] and presumed that the interaction of positively charged oily droplets with negatively charged surface components of the GIT. It was observed Cremophor® EL or RH 40 and TPGS (Tocopheryl Polyethylene glycol 1000 succinate) at concentrations above 0.02%w/v decreased the permeability of CsA due to micellar solubilization[12]. CsA along with paclitaxel co-administration showed more relative bioavailability of the drug in SMEDDS as compared to that of Taxol®. SMEDDS having a delayed positive effect on P-gp inhibitory effect of CsA through increasing oral absorption or enhances the interaction of CsA with Cyt P450 at mature villus tip enterocytes of small intestine[13, 14]. A study with solid SMEDDS also indicated that co-administration of CsA was required in order to increase paclitaxel bioavailability[15, 16]. Saquinavir, a protease inhibitor in highly active antiretroviral therapy (HAART) and is available in both hard gelatin capsule as Invirase® and soft gelatin capsule as Fortovase®[17,18,19]. The hard gelatin capsule exhibited a lower bioavailability than soft gelatin capsule[20] because in soft gelatin capsule formulation contains oil i.e., capmul MCM, a glyceride (medium chain mono and di-glyceride) which can dissolve saquinavir. Amprenavir, a very poorly soluble protease inhibitor and is available as Agenerase® soft gelatin capsule along TPGS, PEG400 and propylene glycol. TPGS enhanced the solubility of amprenavir from 36 to 720 µg/ml and permeability by inhibiting the intestinal efflux[21]. Ritonavir has very low intrinsic water solubility (1.0 µg/ml) with peptide like structure. As it contains two weakly basic thiazole groups with pK_a values of 1.8 and 2.6, ritonavir (Norvir®) hard gelatin capsule is available in market as an amorphous, semi solid dispersion containing solubilized ritonavir with caprylic/capric triglycerides, polyoxyl 35, castor oil, citric acid, ethanol, polyglycolyzed glycerides, polysorbate 80 and propylene glycol. On other hand, a soft gelatin containing ritonavir solubilized with oleic acid, cremophor EL, ethanol and butyl hydroxytoluene (BHT) had portrayed improved bioavailability[22]. Bexarotene, a benzoic acid derivative and selective activator of retinoid X receptor, is available in market for the treatment of T-cell lymphoma. A soft gelatin formulation is available as Targetin® with lipid based excipients of polysorbate 20, PEG 400, povidone and BHA[23]. Combination of lopinavir and ritonavir (80:20) is available as Kaletra® tablets and Kaletra oral solution with Span 20, propylene glycol, cremophor RH 40 and peppermint oil[24].

Composition: This drug delivery system consists of lipids, surfactants, co-surfactants, co-solvents.

Lipids: Lipids are naturally occurring oils and fats, and they are composed with triglycerides and fatty acids of varying chain lengths with degree of unsaturation. Lipids are typically classified according to their chemical structure, polarity, characteristics and degree of interaction with water. Polarity of lipid phase highly influence the drug release in which higher polarity indicate that quick drug release to aqueous phase. A recent study was evident that the rate of idebenone release from its SMEDDS is duly depended on the polarity of oil phase used in which highest release was obtained with Labrafil 2609 with HLB>4[25]. Glyceride fractions of natural lipid oils are used to minimize the oxidation prepare. Hydrophilic forms containing solid formulations exhibit low bioavailability as their absorption is dissolution and capacity-limited due to poor solubility. Oil has main role in solubilizing the lipophilic drug (or) facilitates self emulsification. Stability of the emulsion mainly depends on the rheological behavior of oil. Non digestible lipids such as mineral oil, e.g. liquid paraffin and sucrose polyesters, essentially remain unabsorbed in the intestinal lumen and can limit or even reduce drug absorption by retaining a considerable amount of co-administered drug. Digestive lipids comprise dietary lipids such as glycosides, fatty acids, phospholipids, cholesterol esters as well as various synthetic derivatives. The rate and extent of digestion, the colloidal phases formed and pharmacological effects of the digestion products represent potential factors influencing release of the API from the vehicle and its absorption[26].

SURFACTANTS:

Surfactants are mainly used to improve the bioavailabilty. In the case of ricinoleic acid, due to the presence of hydroxyl group on the 12th carbon of ricinoleic acid, glycerides containing fatty acid (Cremophor® EL) exhibits ethoxylation and increases the hydrophilicity, and bioavailability. Surfactants can improve drug dissolution, enhance intestinal epithelial permeability and increase tight junction permeability[27]. Surfactant in the formulation plays a predominant role to increase absorption of lipophilic drugs.

Mechanism: Interference of lipid bilayer of epithelial membrane with unstirred aqueous layer, forming the rate limiting barrier to drug absorption or diffusion[28, 29] and thereby inhibit the Cytochrome P450[30]. Lipophilicity of the surfactant shows the impact on the emulsion that is formed after lipid digestion.

Surfactants with HLB>10 form finer and uniform droplets in microemulsion when compared to lipophilic surfactants with low HLB values. In many cases both the combinations of low and high HLB surfactants leads to form stable microemulsions[31, 32, 33]. Most commonly used surfactants for self emulsifying formulations are water

soluble in nature[34]. These are ester amphiphilic compounds with medium to high HLB depending upon type and degree of esterification[35, 36]. Chemistry and the nature of interaction of lipid digestion products with the aqueous contents of GI-tract changes related to digestion and solubilisation. Solid dosage form of lipid formulations may improve stability, but having lower drug loading and higher potential for drug crystallization. If so surfactants can control the phase transformations within the formulations. Ethoxylated lipid surfactants such as Gelucire®, Labrasol® and Cremophor® had proved that they inhibit the P-gp modulated drug efflux[37, 38, 39].

Co-surfactants: Co-surfactants with HLB value 10-14 is used along with surfactant for lowering the interfacial tension, interface would expand to form fine dispersed droplets. Fluid interfacial film is achieved by the addition of a cosurfactant. Co-surfactant will enhance the fluidity of the interface and thereby increasing the entropy of the system[40].

Co-solvents: Most of the marketed drug products are with co-solvents for the purpose of solubilizing the drugs[41] and triglyceride in the composition. This enables the dissolution of large quantities of either hydrophilic surfactant or drug in the lipid base. They even act as co-surfactants in microemulsions. Some limitations for the usage of co-solvents includes; immiscibility of some cosolvents with oils, incompatibilities of low molecular weight solvents with capsule shells[42] and precipitation of solubilized drug from solvent due to loss of solvent capacity following dilution[43]. Alcohols and other volatile cosolvents exhibit evaporation especially in the hard gelatin, soft gelatin capsules in conventional SEDDS leading to precipitation, so that alcohol free formulations have been designed.

Methods used in the formulation of SMEDDS:

Dilution method: In this method, surfactant composition is varied in different ratios and the mixture containing oil phase and surfactants were diluted with water and allow it for centrifugation and then filtrate was taken and diluted with ethanol and assayed accordingly for determining the free drug concentration in the vehicle[44].

Water Titration method: Titration method is employed to construct phase diagram, mixture of oil, surfactant and co-surfactant were added to the drug and is placed in a vial, then all the components were mixed by gentle stirring and vortex mixing and this is heated at 40ºC on a magnetic stirrer, until drug is dissolved[45].

Mechanism of lipid based drug delivery system:

GI lipid digestion consists of three steps: (i) The dispersion of fat globules to yield a fine emulsion, (ii)The enzymatic hydrolysis of fatty acid esters at the emulsion-water interface, and (iii) Desorption and dispersion of insoluble lipid products for subsequent absorption. These systems may enhance the absorption from the gastrointestinal tract. Reduction of particle size to molecular level facilitates the solubilization process[46, 47] changing drug uptake, efflux and disposition by enterocyte based transport[48] and increasing drug transport to the systemic circulation via intestinal lymphatic system[49]. Lipophilic drug absorption can occurs by the lipids into the portal blood. Triglycerides and long chain fatty acids play a major role in prolonging the GIT residence time. Although a high fat meal elevates the TG-rich lipoproteins which react with drug molecules. Combination of lipoproteins with drug enhances the intestinal lymphatic transport and changes in drug disposition and also in pharmacological actions of poorly soluble drugs[50].

SELECTION OF EXCIPIENTS:

Self emulsification shows the specific nature of the oil/surfactant ratio, the surfactant concentration and the temperature at which self emulsification occurs. Pharmaceutical excipient combinations lead the efficient self emulsifying systems[51, 52]. These components are meant for achieving maximum drug loading, minimal self emulsification time and droplet size in the gastric milieu for obtaining maximum absorption, to reduce variation in the emulsion droplet size and to prevent or minimize drug degradation. For selection of a suitable self emulsifying vehicle the following are to be addressed: a) The drug solubility in various components, b) The area of self-emulsifying region in the phase diagram and c) Droplet size distribution following self-emulsification[53].

Solubility: Solubility is a useful tool for the selection of a solvent or solvents for a particular application. Solubility parameters estimate the compatibility between two components. Hildebrand solubility parameters are effective to predict the formulation characteristics.

Hydrophilic-Lipophilic Balance (HLB): The HLB is an empirical formula that is used to characterize surfactants and to select those appropriate for preparation of microemulsions of a particular compound[54, 55].

Partition Coefficient: The lipophilicity of a molecule related to the partition coefficient of a compound between a lipophilic and a hydrophilic phase, is also an important factor in the selection of excipients[56]. Compounds with log P>4 (i.e., being more lipophilic) are likely to be dissolved in oils and the compounds with intermediate log P (log P<4) may require a mixture of hydrophilic surfactants (HLB 4-12) or water-soluble co-solvents to form a self-emulsifying system with maximum solubility. Compound with low log P shows highest solubility in oil phases while a compound with high log P does not show highest solubility in oil[57].

Structure based excipients:

Triglycerides: These are the most commonly used lipid based drug delivery excipients. In this ester groups are present which are majorly fatty acid triesters of glycerol[58]. The pure triglycerides are mainly present in refined vegetable oils[59]. When compared with long chain glycerides, medium chain glycerides show complete digestion and also high solvent capacity[58]. Long chain fatty acids and monoglycerides are re-esterified to triglycerides within the intestinal cell, incorporated into chylomicrons and secreted from the intestinal cell by exocytosis into the lymph vessels by resynthesized triglycerides accumulation within the Golgi apparatus. Chylomicrons are formed by the addition of phospholipids and proteins. These chylomicrons in the

Golgi vesicles are secreted into the intercellular spaces by exocytosis, and then travel through the lamina propria to lymphatics.

Surfactants: Surfactants are the compounds that lower the surface tension of a liquid. These surfactants diffuse in water and absorb at interface between oil and water, Hydrophilic-lipophilic balance (HLB) of the surfactant can be considered as an important factor for surfactant's behavior. Surfactant with HLB values from 3-6 forms the water-in-oil (w/o) microemulsions, whereas surfactants with HLB value from 8-18 forms oil-in-water (o/w) microemulsions. Oil-in-water microemulsions were droplets of oil surrounded by a surfactant film that forms the internal phase distributed in water, which was the continuous phase. Unsaturated ester based surfactants are highly efficient in the formation of self emulsification than the saturated ether based surfactants.

Water-insoluble surfactants: These are the group of lipid excipients having intermediate hydrophilic-lipophilic balance (HLB of 8–12) that adsorb at oil–water interfaces and are hydrophilic in nature and forms self emulsification. Oleate esters such as polyoxyethylene sorbitan trioleate (Tween-85), polyoxyethylene glyceryl trioleate (Tagot TO) are examples of water-insoluble surfactants having HLB values are between 11 and 11.5, based on the degree of ethoxylation, these are soluble in water and forms dispersion[60].

Water-soluble surfactants: These are the most commonly used surfactants in the formulation of self-emulsifying drug delivery systems. These are water soluble having HLB value of 12, low concentration of this forms micellar solutions in pure water above their critical micellar concentration. Alcohols can be made to react with ethylene oxide to produce alkyl ether ethoxylate, which is a commonly used surfactant e.g., cetostearyl alcohol ethoxylate (cetomacrogol). Sorbitan esters react with ethylene oxide produces polysorbates (ether ethoxylates), Cremophor RH40 and RH60 (ethoxylated hydrogenated castor oil)**,** this enhances the absorption by inhibiting the efflux pumps[61, 62].

Analysis of excipients in lipid based drug delivery system:

Chemical Analysis: Composition of lipid based excipients i.e., esters, ethers and distribution of fatty acid can be assayed by HPLC and GC methods. For hygroscopic or high HLB value excipients moisture content must be analysed[63].

Physical Analysis: Lipids have higher chemical composition and leads to broad melting point as opposed to a single melting point. DSC (Differential scanning calorimetry) used for the study of thermal behavior of excipients like melting, crystallization, solid to solid transition temperatures. Solid fat content of the excipient related to temperature can be assayed by nuclear magnetic resonance (NMR). Crystallinity of a lipid excipient can be determined by XRD[63].

Analysis of physiological effects of excipients: Oral absorption had various physiological effects such as retarding gastric emptying[64] and stimulation of bile flow, secretion of pancreatic juice[65], enhancing the membrane lipid fluidity or acting directly on to the enterocytes based drug transport and disposition[66], inhibiting efflux transporters like p-glycoprotein (P-gp) *in-vitro* models assess these effects by using liver and intestinal slices[67]. These effects occurred due to the increase in the oral absorption by lipid based excipients.

DELIVERY OF PROTEINS AND PEPTIDES BY LBDDS:

This lipid based drug delivery system composed of polar lipids such as phospholipids, medium chain fatty acid and its derivatives like medium chain triglycerides (Miglyol 812, Captex 355.) These are less lipophilic than long chain lipids (soyabean oil, sesame oil), thus able to emulsify easier than long chain glycerides. Lipid based delivery systems are mainly employed for the delivery of peptides and protein drugs. In this peptides and proteins are encapsulated into the aqueous phase of the emulsion based systems, and achieves high drug loading[68]. It was studied that SMEDDS with high entrappment efficiency of 99.2% was prepared by dispersing the concentrated insulin solution i.e., (60 mg/ml) into the oil phase (PEG-8 glyceryl caprylate/caprate) this enables the delivery of insulin[69]. Liposomes are effectively suitable for the delivery of peptides and proteins by surface modification and biocompatibility, these delivers the peptides and proteins[70]. Lipid nanoparticles are new and innovative model for the delivery of recombinant proteins[71]. The studies so far carried out on SMEDDS were listed in table no1.

CONCLUSION:

Lipid based dosage formulations are potential for formulating lipophilic drugs for their solubility and to improve bioavailability. The efficiency of LBDDS is highly depended on the excipients selected and used in the formulations. Therefore the selection and composition of excipients such as lipid/oil, surfactant and co-surfactant/co-solvent are critical issues in the LBDDS design and development. The review carefully highlighted the required features of excipients to be used in LBDDS. The criterion to select excipients such as phase diagram and mechanism of microemulsion formation was explained with suitable examples. The formulation of SMEDDS was compared with the marketed formulations and their compositions are drawn. This review article provides very useful information about excipients, formulation aspects of microemulsions, self emulsifying systems, characterization, compositions of commercially available SMEDDS with special emphasis to excipient role/functions. Thus this review enables the researchers for careful and suitable selection of excipients, quantities of excipients, methods to be employed for handling of potent and immunogenic moieties such as peptides and proteins.

Table 1: Summary of past work on SMEDDS with improved therapeutics[72-94]

Compound	Study design	Formulation	Result/Response	Reference
Oleanolic acid	SMEDDS for improved oral B.A.	Cremophor Ethanol Ethyl oleate	Relative B.A increased by oleanolic acid when compared to marketed formulation.	72
Pranlukast hemihydrate	SMEDDS for improved oral B.A of pranlukast hemihydrate	Cremophor EL Triethyl citrate Benzyl alcohol Tween 20 Span 20	SMEDDS formulation of this shows B.A, increased by three fold when compared to plain PLH aq. suspension.	73
Exemestane	Oral B.A enhancement of exemestane SMEDDS.	Castor oil Cremophor EL Capryol 90 Transcutol P Labrasol Lauroglycol	SMEDDS formulation increases the 2.9 fold B.A when compared with marketed formulation.	74
Simvastatin	Development of SMEDDS for oral B.A, enhancement of simvastatin beagle dogs.	Capryol 90 Cremophor EL Carbitol	Relative B.A in dogs/B.A is 1.5 fold increased from SMEDDS formulation.	75
Silymarin	Enhanced B.A of Silymarin by SMEDDS.	Tween 80 Ethyl alcohol Ethyl linoleate	B.A increased by 2 fold from SMEDDS formulation	76
Candesartan cilexetil	Formulation and evaluation of SMEDDS of candesartan cilexetil	Transcutol P Capryol 90 Plurol oleique	Optimized formulation shows rapid self emulsification in aqueous media so that this SMEDDS formulation improves the B.A of drug.	77
Pueraria Lobata Isoflavone (Herb)	SMEDDS for improving Invitro dissolution and oral absorption of Pueraria Lobata Isofalvone.	Tween 80 Transcutol P Ethyl oleate	Relative B.A increased by 2.5 fold in SMEDDS when compared to marketed formulation (tablets).	78
β-Artemether	SMEDDS using natural lipophile, Application to β-Artemether delivery.	Capryol 90 Natural_LCT Cremophor EL Tween 80 Gelucire 44/14 Plurol oleique CC97	SMEDDS with β-Artemether improves the anti-malarial activity by enhancing the absorption of drug	79
Sorafenib	Preparation of sorafenib SMEDDS and its relative B.A in rats	Ethyl oleate CremophorEL PEG 400 Ethanol	Relative B.A of this is increased by SMEDDS when compared to Sorafenib Suspension.	80
Tacrolimus	SMEDDS of tacrolimus formulation and invitro evaluation and stability studies.	Lauroglycol FCC Cremophor RH PEG 400	SMEDDS increases the oral B.A of tacrolimus and the optimized formulation of this inhibits Cyp metabolism and P- gp efflux.	81
Curcumin	SMEDDS improves curcumin dissolution and B.A	Ethanol Isopropyl Myristate Cremophor RH40	Relative B.A of curcumin Microemulsion shows 12 fold higher when compared to suspension and SMEDDS formulation increases the B.A of the curcumin.	82
Probucol	SMEDDS for improved oral B.A of Probucol: preparation and evaluation.	Olive oil Lauroglycol FCC Cremophor EL Tween 80 PEG 400	Relative B.A of SMEDDS formulation enhanced by 10.2 folds that of oil solution and suspension.	83
Valsartan	Preparation and B.A assessment of SMEDDS containing valsartan.	Captex 200P Capmul MCM Tween 80 Cremophor EL PEG 400	B.A of valsartan is enhanced by SMEDDS formulation when compared with marketed formulation.	84
Glyburide	SMEDDS Of glyburide formulation In vitro Evaluation and stability studies	Capryol 90 Transcutol P Cremophor EL Tween 20 Tween 80	SMEDDS with glyburide shows increase in the dissolution rate when compared with glyburide marketed formulation and pure glyburide powder.	85
Domperidone	Development of SMEDDS of Domperidone:Invitro and invivo characterization.	Labrafac CC Tween80 Transcutol P	Oral B.A study shows that, this SMEDDS formulation increases the B.A by 1.92 fold when compared to that of suspension.	86
Felodipine	Design and Optimization of Felodipine for Chronotherapeutic application.	Lauroglycol FCC Cremophor EL Transcutol P	This SMEDDS formulation shows lag time of 5-7 hrs. So that it is desired for chronotherapeutic application.	87
Penfluridol	Formulation and Physicochemical Characterization of a novel SMEDDS as hydrotropic and solubilising agent for Penfluridol.	MCT(medium chain Triglyceride) Cremophor EL PEG 400	Optimized SMEDDS shows more solubilization.	88
Vinpocetine	SMEDDS of Vinpocetine: Formulation Development and *In-vivo* Assessment.	Oleic acid Labrafac Cremophor EL Transcutol P	SMEDDS of this drug shows improved oral B.A. of vinpocetine.	89
Nimodipine	A new S-SMEDDS formulation prepared by spray drying to improve the oral B.A. of poorly water soluble drugs.	Ethyl oleate Cremophor RH 40 Labrasol	Absorption rate of the drug is enhanced by Solid SMEDDS when compared with that of liquid SMEDDS.	90
Lingusticum chaunxiong (Rhizome)	Preparation, Characterization and evaluation of SMEDDS of Lingusticum chaunxiong oil	Olive oil Oleic acid Ethyl oleate Cremophor EL	Insitu absorption shows SMEDDS improves the absorption rate of the drug.	91
Curcumin	Novel Plug controlled Colon-specific Pulsatile Capsule with tablet of Curcumin loaded SMEDDS.	Ethyl oleate Transcutol P Cremophor RH 40	This study shows that tablets in impermeable capsules have more potential for delivery of poorly water soluble drugs to colon.	92
Orlistat	Design, Development and Optimization of SMEDDS of anti-obesity drug	Propylene glycol laurate Propylene glycol mono caprylate Polysorbate 80	SMEDDS formulation of this shows more drug release when compared with marketed formulation.	93
Furosemide	Oleic acid based heterolipid synthesis, Characterization and application in SMEDDS.	Heteolipid Solutol HS 15® Ethanol	In this formulation Heterolipid acts as an oil phase mainly for the delivery of the drug through I.V. route.	94

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