WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 8, Issue 5, 749-772. Review Article ISSN 2277– 7105

ENHANCEMENT OF AQUEOUS SOLUTION AND BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS BY SELF EMULSIFYING DRUG DELIVERY SYSTEM

Aravindh Govindharasu*[1], Elango K.[2] and Deattu N.[3]

Department of Pharmaceutics, College of Pharmacy, Medras Medical College, Chennai, Tamilnadu, India.

Article Received on
08 Feb. 2019,

Revised on 02 March 2019,
Accepted on 23 March 2019

DOI: 10.20959/wjpr20195-14632

***Corresponding Author**
Aravindh Govindharasu
Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai, Tamilnadu, India.

ABSTRACT

The Self emulsifying Drug Delivery System (SEDDS) is a Novel Drug Delivery System for Enhancement of water solubility of poorly water soluble drugs. It is isotropic mixture of oil, surfactant, co-surfactant molecules and it also containing co-solvent molecule. It is Drug delivery system is thermodynamically and kinetically stable. The drug delivery system under mild agitation is followed by dilution of aqueous media such as GI fluid and it can from stable O/W emulsion. It is important type of Drug delivery system to maintain the chemical stability as well as solubility of drug product. The Self emulsifying Drug Delivery System (SEDDS) is important application on BCS Class II and Class IV Drugs for improving water Solubility of poorly water soluble drugs. It is important to prevent the interfacial tension and improving the dissolution as well as absorption rate of drug molecule. It is Novel Drug Delivery System is Applicable for parenteral, Ophthalmic, intranasal and cosmetic drug delivery system.

KEYWORDS: Nanoemulsion, Microemulsion, Surfactant, Self-emulsifying system, Improving water solubility, Bioavailabillity enhancement.

INTRODUCTION

In the last 2 decades, many tools in drug discovery and screening were rapidly developed. Examples are automated synthesis, combinatorial chemistry, molecular genetics and high-throughput screening (HTS) methodologies. Accordingly, a large number of compounds has been identified as potential drug candidates.[1-4] Lipinski *et al.*[1, 2] have proposed the "rule of

5" to identify the potential poorly bioavailable drug candidates. Proposed properties of poor bioavailability include: (a) high molecular weight (> 500 D), (b) high lipophilicity (Log P > 5 or MLogP[1] > 4.15), (c) possession of more than 5 H-bond donors (e.g. NHs and OHs) and (d) possession of more than 10 H-bond acceptors (e.g. Ns and Os). This rule is only valid for drug candidates that are not substrates for active transporters and efflux mechanisms. Poor bioavailability is always originated from poor aqueous solubility (a and b) or poor intestinal permeability (a, c and d).[5]

Amidon *et al.*[6] have introduced the Biopharmaceutics classification system (BCS). BCS provides a classification of drugs according to their maximum dose solubility, dissolution and permeability into four classes (**Fig. 1**).

Unfortunately, the number of potential drug candidates, especially those with high molecular weight and high Log P, is progressively increasing. Accordingly, the problem of the poor aqueous solubility (< 1 µg/ml) has become dominant in the pharmaceutical industry.[1,2] Recent studies showed that ~75 % of the drug development candidates are poorly water-soluble. This ratio could be increased to 80-90 % depending on the therapeutic area.[10,11] As a result, they may fail to reach the market despite their pharmacological activity. Poorly water-soluble drugs (PWSDs) represent Class II and IV of the BCS[6] and could be classified as grease balls and brick dusts.[12] Brick dusts have a low to moderate lipophilicity and high melting point (> 190 °C) because of their strong, stable lattice structure. Their strong intermolecular bonds hinder their solubility in water. On the other hand, grease balls are highly lipophilic compounds (log P > 4) with lower melting point (< 190 °C). They are not able to form bonds with the water molecules.[13] Since drugs are absorbed in the dissolved state, several problems are associated with PWSDs such as inter- and intra-patient variability as well as reduced bioavailability. Furthermore, PWSDs dose is always augmented to reach the therapeutic blood level. This leads to local GI tract irritation, toxicity, patient incompliance, higher costs as well as inefficient treatment.[14]

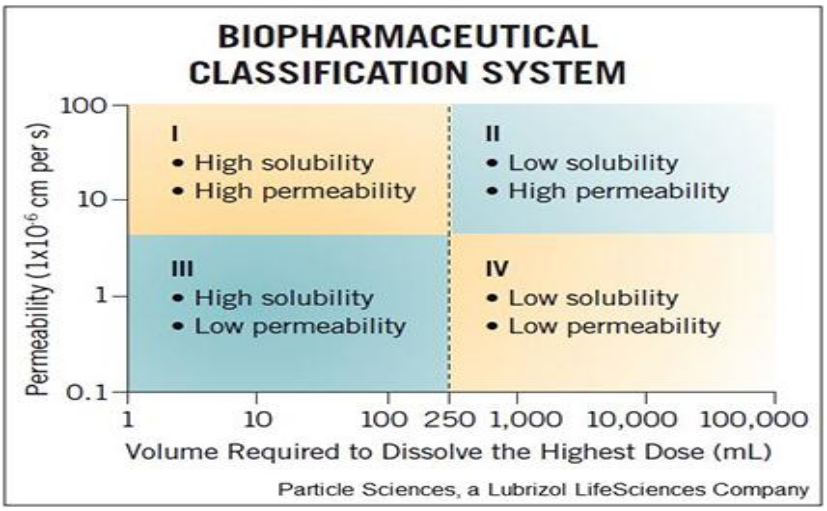

Fig. 1: Biopharmaceutics classification system of drugs (BCS).

Several strategies have been developed to enhance the water solubility and hereafter the bioavailability of PWSDs. These strategies could be briefly summarized into: (a) Physical modifications such as particle size reduction, optimization of crystal habit, co-crystal formation and solid dispersions. (b) Chemical modifications such as the use of buffers, salt formation and complexation (Cyclodextrins). (c) Miscellaneous methods such as the use of surfactants, co-solvents, hydrotrophy, supercritical fluids and lipid-based drug delivery systems (LBDDS).[3,4,9,15]

Lipids represent a large class of compounds that can be classified according to their chemical structures, origin, solubility in organic solvents or biochemical interactions.[16] A pioneer in the field of lipid-based systems, Small[17], has introduced a lipid classification system based on lipid/water interactions in bulk water and the behavior of lipids at the air/water interface (**Table 1**).[19]

LBDDS bioavailability enhancement is ultimately beneficial in the case of grease balls PWSDs, which have adequate solubility in pharmaceutical lipids (Log P > 4).[19,20] Examples of LBDDS include lipid solutions, lipid suspensions, liposomes, liquisolids, solid lipid nanoparticles (SLN), nanostructured lipid carriers (NLC), mixed micelles, nanocapsules, liquid crystalline nanoparticles (LCNP) (e.g. Cubosomes®, Flexisomes® and Hexosomes®), emulsions, nanoemulsions, microemulsions, and self-emulsifying drug delivery systems.[21,22]

Table 1: Lipid classification system proposed by Small.[17]

Class	Bulk interactions with water	Surface interactions with water	Examples
Non-polar	- Insoluble - Crystals or oil	Do not spread to form a monolayer	Cholestanes, benzpyrenes, carotenes, lycopenes and gadusenes
Polar I	- Insoluble, non-swelling - Crystals or oil	Form a stable monolayer	CS, TG, DG, long chain protonated FA, waxes, sterols, oil soluble vitamins and steroidal hormones
Polar II	- Insoluble, swelling - LC	Form a stable monolayer	PL, MG, FA soaps and cerebrosides
Polar IIIA	- Soluble with lyotropic mesomorphism - Crystals or oil → LC →Micelles	Form an unstable monolayer	Lysolecithins and surfactants
Polar IIIB	- Soluble without lyotropic mesomorphism - Crystals or oil → micelles	Form an unstable monolayer	BS and saponins

CS: cholesterols; TG: triglycerides; DG: diglycerides; FA: fatty acids; PL: phospholipids; LC: liquid crystals; BS: bile salts.

LBDDS present and maintain the drug in the solubilized form, in which absorption takes place.[26,27] As a result, the rate-limiting step of drug dissolution is eliminated. Furthermore, they can enhance the bioavailability by different mechanisms depending on their type and amounts such as prolongation of the gastric emptying time; stimulation of bile secretion and interaction with bile salts (BS), phospholipids (PL) and cholesterol (CS) mixed micelles; reduction of the first pass metabolism via stimulation of intestinal lymphatic transport for highly lipophilic drugs (Log P > 5) and reduction of the enterocyte-based metabolism; modulation of intestinal efflux transporters such as P-glycoprotein; permeation enhancement; as well as generation and maintenance of a metastable supersaturable drug state.[27-29] Oral administration of lipids stimulates the secretion of the gastric lipase (HGL) with the consequent secretion of the pancreatic lipase (HPL) and co-lipase from the pancreas along with other esterases such as phospholipase A2 (PLA2), carboxyl ester hydrolase (CEH) and pancreatic lipase related protein 2 (PLRP2).[30,31] Most of the lipid excipients are esters.

Examples are glycerides, PEG esters of fatty acids, polysorbates, PL and CS esters. Ester bonds are generally potential substrates to lipolytic enzymes. Examples of lipid digestion products of different lipid classes are summarized in **Table 2**.

Table 2: Enzymatic lipolysis of different lipid excipients.[31]

Lipid class	Lipolytic enzyme(s)	Digestion products
Glycerides	HPL > HGL	TG → DG + FA → 2-MAG + FA
	CEH, PLRP2, HGL	2-MAG → FA + glycerol
PEG esters	CEH >> PLRP2 > HGL	PEG DE → PEG ME + FA → PEG + FA
Phospholipids	Phospholipase A2	Phospholipids → Lyso-1-phospholipids + FA
	PLRP2 > CEH	Phospholipids → Lyso-2-phospholipids + FA
Galactolipids	PLRP2 > CEH	DGDG → DGMG + FA
Cholesterol esters	CEH	Cholesterol ester → cholesterol + FA

HPL: human pancreatic lipases; HGL: human gastric lipases; HTG: triglycerides; DG: diglycerides; FA: fatty acids; 2-MAG: 2-monoacylglycerols; CEH: carboxyl ester hydrolase; PLRP2: pancreatic lipase-related protein 2; DE: diesters; ME: monoesters; DGDG: digalactosyldiglycerides; and DGMG: digalactosylmonoglycerides.

Lipid digestion usually inaugurates in the stomach by the action of HGL.[32] HGL is an acid stable lipase with an optimum activity at pH 3-6 and a maximum activity at pH 5.0-5.4.[25,30-33] HGL works on the lipid/water interface. Therefore, the ingested lipids need to be emulsified before being digested. The emulsification is usually achieved by the shear action of the stomach along with the surface active actions of the co-administered amphiphiles and digestion products such as monoglycerides (MG) and dietary proteins.[31] In some cases such as incomplete pancreatic function (neonates) or compromised one (cystic fibrosis or chronic alcoholism), gastric lipolysis plays the principal role in the lipid digestion.[32, 34] However, in most cases, gastric lipolysis accounts only for 10-25% of the total lipid lipolysis.[35, 36]

HPL is produced in the acinar cells of the pancreas and is secreted along with bile under the stimulation of cholecystokinin and secretin. HPL is active only above pH 5 with a maximum activity at pH 7.0-7.5.[33] Similar to HGL, HPL works on the lipid/water interface. HPL is a regioselective enzyme that hydrolyze only sn-1 or sn-3 positions. On the other hand, HGL can hydrolyze the 3 ester positions.[33] Other lipolytic enzymes such as CEH, PLA2 and PLRP2 do not work on the interface. They hydrolyze the lipid excipients in the dispersed micelles or mixed micelles.[31] Therefore, they are beneficial in the digestion of various lipid excipients.[43] Examples are summarized in **Table 2**.

The interaction of the lipids with the bile mixed micelles plays a crucial role in the lipid lipolysis process as well as the biofate of the accompanied PWSDs. Lipid/bile interactions vary from the adsorption of BS on the lipid/water interface of the less polar lipids droplets

(TG and DG) to the formation of various colloidal structures such as micelles, mixed micelles and vesicles (**Fig. 2**) with more polar lipids (2-MAG and FA).[46] Furthermore, BS clean the lipid/water interface by displacing other amphiphiles such as proteins and incorporating of the digestion products, especially long chain 2-MAG and FA, into their mixed micelles. Otherwise, accumulation of the digestion products at the interface would inhibit the action of HPL.[31,47] On the other hand, the digestion products of medium chain lipids are more polar and do not need the action of BS to be dispersed in the aqueous media.

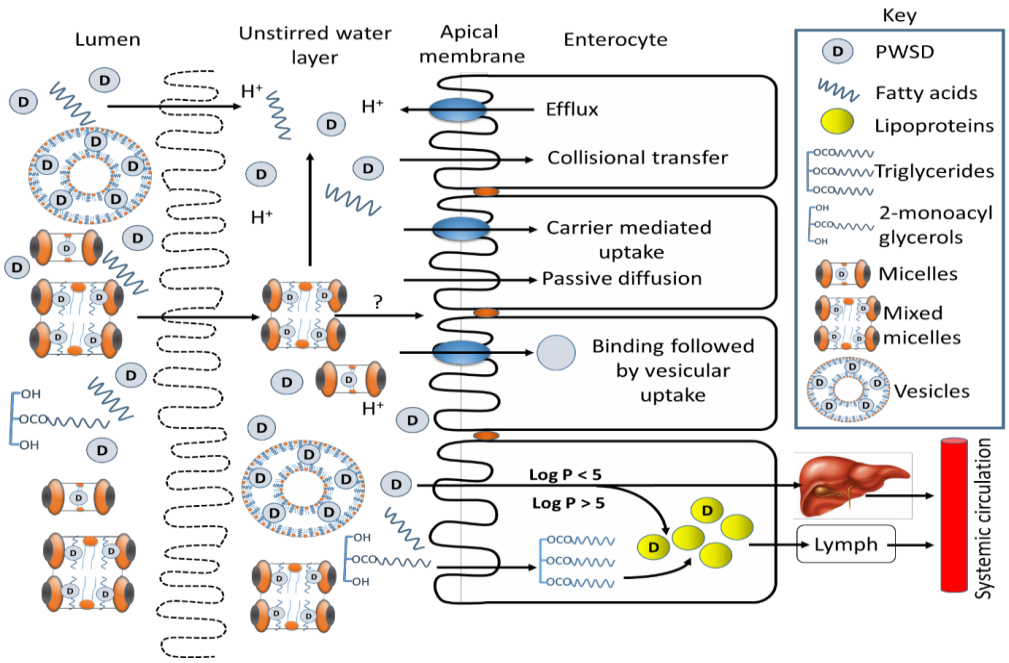

Fig. 2: Schematic representation of different mechanism of lipids and drugs absorption as well as lipid-mediated bioavailability enhancement.[27]

The biofate of the PWSDs is strongly dependent on the LBDDS dispersion pattern, digestion as well as the interaction of their dispersions and digestion products with the bile mixed micelles rather than the properties of the LBDDS themselves.[25,27] During lipid dilution and digestion several liquid crystalline (LC) and colloidal phases might occur that have different PWSDs solubilization capacity.[46] The incorporation of the digestion products into the bile mixed micelles strongly increases their PWSDs solubilization capacity. However, this increase is dependent on the FA chain length (long chain > medium chain), the nature of the colloidal dispersions (vesicles > micelles) and the phase behavior of the digestion products (cubic phases > lamellar phases > colloidal phases) as well as the PWSDs lipophilicity.[48, 49] However, some exceptions were also reported.[25] Furthermore, the incorporation of PWSDs, FA and 2-MAG into the bile mixed micelles enhances their mass

transfer along the unstirred water layer (UWL).[50,51] (UWL) represents the physical barrier between the bulk fluids in the intestinal lumen and the apical membrane of the enterocyte, where the absorption takes place (**Fig. 2**). UWL has an aqueous acidic microenvironment.[52] Therefore, protonated FA and PWSDs are slowly diffused through it. On the other hand, micelles have higher solubility in the UWL. However, it seems that micelles do not be absorbed intact into the enterocyte[53] as the acidic microenvironment within the UWL accelerates its dissociation.[54] The absorption of the PWSDs and lipids (FA and 2- MAG) into the enterocyte could occur by passive diffusion or carrier-mediated uptake. Furthermore, colloidal structures could be also absorbed by collisional transfer as well as carrier- or vesicular- mediated uptake (**Fig. 2**). However, the absorbed PWSDs and FA could suffer from the action of the efflux transporters that efflux them back into the UWL.[27]

The absorbed lipid digestion products could be directly transported into the portal circulation with a subsequent first pass metabolism. Alternatively, FA and 2-MAG are re-esterified in the endothelial reticulum into TG that constitutes along with CS esters the hydrophobic core of lipoproteins such as chylomicrons and very low-density lipoproteins (VLDL) (**Fig. 2** bottom). After exocytosis into the interstitial spaces, lipoproteins are selectively taken up by the lymphatic system rather than the blood vessels. The transport of FA into the portal circulation or the lymph may depend on its chain length, degree of unsaturation as well as the class of the administrated lipids. However, in some cases contradictory data are reported.[56] Based on their number of carbon atoms, FA could be classified as short (4-6), medium (8- 12), long (14-18) or very long chain (20-24).[57] In most cases, short and medium chain FA are directly transported to the portal circulation while long chain FA are usually involved in the lipoproteins synthesis. Furthermore, increasing the degree of FA unsaturation was found to promote their lymphatic uptake.[58] Highly lipophilic absorbed PWSDs (Log P > 5 and TG solubility > 50 mg/g) might be incorporated into lipoproteins (**Fig. 2** bottom).[59] The transportation of PWSDs along the lymphatic system offers some advantages such as the avoidance of the first pass metabolism, reduction of the enterocyte metabolism[60] and the possible drug targeting (in the case of anticancers and immunomodulators).[61] However, high PWSD concentration in the lymphatic system may cause local toxicity.[27]

Vast varieties of possible lipid excipient combinations are available. Therefore, a classification system was developed to stratify lipid-based formulations into those that could display similar *in vivo* performance. Pouton[9,19] has established the lipid formulation

classification system (LFCS). He itemized LBDDS into five categories (**Table 3**) based on their composition and the possible impact of dilution and digestion on the biofate of the lipid carrier and the drug. Class I formulations are the most lipophilic and are generally regarded as safe. This might introduce a variability and food dependency. On the other hand, Class IV formulations are oil-free and rather polar systems based on surfactants and co-solvents. In general, they are less sensitive towards digestion but more sensitive towards dilution.[62]

Table 3: Lipid formulation classification system (LFCS) proposed by Pouton[9] showing the typical compositions and the properties of the LBDDS.

Excipient	Content in the formulation (% m/m)				
	Class I	Class II	Class IIIA	Class IIIB	Class IV
Oils: MG, DG and TG	100	40-80	40-80	> 20	———
Water-insoluble surfactants (HLB < 12)	———	20-60	———	———	0-20
Water-soluble surfactants (HLB > 12)	———	———	20-40	20-50	30-80
Hydrophilic co-solvents	———	———	0-40	20-50	0-50
Lipophilicity					
Dispersibility					
Digestibility					
Effect of dilution					

Self-emulsifying drug delivery systems represent class II and class III of the LFCS. They are composed of two or more ingredients, which provide the self-emulsifying properties: more hydrophilic amphiphiles, more lipophilic amphiphiles and sometimes co-solvents or precipitation inhibitors. Upon mild agitation and dilution in the GI fluids, these systems transform into oil in water (O/W) emulsions (SEDDS), double emulsions (SDEDDS), microemulsions (SMEDDS) or nanoemulsions (SNEDDS).[15,63] Microemulsions are thermodynamically stable while nanoemulsions are only kinetically stable. However, in most of the literatures, SNEDDS and SMEDDS are usually subjectively assigned to formulations that provide fine colloidal dispersions.[23,64]

Self-emulsification increases the bioavailability by the circumvention of drug crystal

dissolution, which is often insufficient and highly variable for the PWSDs.[65] Compared to the conventional emulsions, SNEDDS are water-free systems. Accordingly, they have better physical and chemical stability. SNEDDS have high patient compliance and palatability as they are always formulated as capsules or tablets. Food has minor effect on drug absorption from SEDDS compared to other LBDDS. Other advantages include the ease of manufacture and scale-up as well as quick onset of action.[19] In addition, being a mixture of more lipophilic and more hydrophilic amphiphiles, SEDDS offer high solubilization capacity to a wide spectrum of PWSDs with different degrees of lipophilicity compared to other LBDDS.[66]

SEDDS are not only restricted for the oral use.[68-71] Self-emulsifying suppositories[72], intraurethral liquid formulations[73], injections[74], implants[75], transdermal[76] and ocular systems[77] were also reported.

The mechanism of the self-emulsification process is still not clear. However, Reiss[78] have suggested that self-emulsification occurs when the entropy change in the favor of dispersion is higher than the energy required to increase the surface area of the dispersion. The free energy of an emulsion is a function of the energy required to create a new surface between the oil and water phases that could be described by the following equation:

$$\Delta G = \sum N\pi r2\ \sigma$$

Where **G** is the free energy associated with the process, **N** is the number of droplets, **r** is the radius of the droplets and σ is the interfacial energy. The free energy of mixing is ignored.

Crude emulsions are not thermodynamically stable. Therefore, oil and water phases have a high tendency to separate in order to reduce the interfacial energy. The presence of the more hydrophilic amphiphiles stabilizes the interface and reduces the interfacial free energy by formation of a monolayer around the oil droplets. In the case of the SNEDDS, the free energy required to form the emulsion is very small and could be positive or negative.

Therefore, the emulsification process takes place spontaneously.[69] The easiness of the emulsification was proposed to be related to the ease of water penetration into the various LC or gel phases formed on the surface of the droplets.[21] The interface between the oil and the aqueous continuous phase is formed upon addition of the oil/hydrophilic amphiphiles mixture to the water. Water penetrates then into the interface and is solubilized in the oil phase. The extent of water penetration is dependent on its solubilization limit close to the interface.[79]

Further aqueous penetration leads to the dispersion of the LC phase. Finally, oil droplets surrounded by LC interface are formed. The extent of the LC interface depends on the hydrophilic amphiphile concentration in the mixture.[21,66, 80, 81]

Several lipid excipients could be formulated as SNEDDS.[24,28,82] Based on their polarity, HLB and interaction with the aqueous media, they could be classified as more lipophilic amphiphiles (Polar lipids I and II) and more hydrophilic amphiphiles (Polar lipids IIIa).

More lipophilic amphiphiles are mostly referred to as oils or fats depending on their physical states at room temperature. They usually offer high PWSDs solubility compared to the more hydrophilic ones. Pharmaceutical lipids could be of natural (**Table 4**), semi synthetic or synthetic origin (**Table 5**). Based on their chain length, medium and long chain lipids are the commonly used oil part of the SEDDS. Short chain lipids are commonly used as co-surfactants to enhance the film flexibility at the interface and to promote nanoemulsions formation. Very long chain lipids are scarcely used in the SEDDS formulations.[15,28, 66]

Table 5: Examples of the commonly used natural lipids in the formulation of SNEDDS. The exact fatty acids composition is tabulated in.[28, 83]

	Examples
Long chain lipids	Apricot kernel, Canola, Castor, Corn, Olive, Palm, Peanut, Safflower, Sesame, Soybean and Sunflower oils
Medium chain lipids	Coconut and Palm kernel oils

More lipophilic amphiphiles are generally regarded as safe. They are mostly composed of a mixture of TG and partial glycerides of FA. Furthermore, propylene glycols, PEG and sorbitan esters of FA as well as free FA (e.g. oleic acid) are commonly used as lipophilic amphiphiles. The solubility of PWSDs in a particular lipid is dependent on the effective ester molar concentration of the lipids.[84] Therefore, the same mass of the medium chain lipids usually afford higher PWSDs solubilization power than long chain ones.[20] Furthermore, depending on their chain length, lipids may have different biofate. The transport through lymphatic circulation, in the most reported cases, is dependent on the lipid chain length (long > medium> short) and the degree of unsaturation.[85] Therefore, the accompanied PWSDs transport through lymphatic system might be enhanced and the first pass metabolism could be reduced when they are incorporated in long chain glycerides. However, the lymphatic transport is also dependent on PWSDs lipid solubility (> 50 mg/g) and lipophilicity (log P > 5). On the other hand, medium chain lipids are usually transported through portal veins to the

systematic circulation. Therefore, the accompanied PWSDs could extensively suffer from the first pass metabolism.[86,87]

More hydrophilic amphiphiles are incorporated to promote the dispersibility of the accompanied more lipophilic ones through the reduction of the interfacial tension. They are usually referred to as surfactants. As surfactants can fluidize or solubilize biological membranes, their toxicity must be greatly considered. The toxicity of surfactants is in this order: cationic > anionic > non-ionic. Esters are considered less toxic than ethers. Furthermore, bulky surfactants are deemed to be less toxic than those with single chain.[20] Therefore, non-ionic, bulk, FA ester polymers are the most commonly used hydrophilic amphiphiles in the formulation of SNEDDS (**Table 6**). Furthermore, the HLB value of the surfactant is very important for the self-nanoemulsifying process. To ensure adequate fast dispersibility, surfactants with higher HLB values (> 12) are normally used.[66]

Miscellaneous excipients such as co-solvents, precipitation inhibitors and antioxidant might be used to improve the SNEDDS performance, PWSD load and the shelf-life stability. Examples are summarized in (**Table 7**). Co-solvents can increase the SNEDDS drug solubilization power. However, the relationship between the drug solubility and the co-solvents concentration is nearly logarithmic. Therefore, the use of co-solvents carries a high risk of PWSDs precipitation upon dilution in the GI fluids.[9,19] Furthermore, co-solvents, especially the volatile ones, have an adverse impact on the capsule shelf-life stability,[4,20,88,89] SNEDDS should not only be able to solubilize PWSDs, but also to maintain drug solubilization throughout the GI tract.[64] Due to its higher co-solvents content, SNEDDS carry a high risk of drug precipitation upon dilution into the GI fluids.[19]

Table 6: Examples of the commonly used semisynthetic and synthetic more lipophilic amphiphiles in the formulation of SNEDDS.[24,28,82]

Excipient name	HLB	Description	Supplier
Medium chain glycerides			
Capmul® MCM	5.5	C8/C10 MG [58 % MG, 36 % DG, 5 % TG; 80 % C8, 20 % C10]	Abitec
Capmul® MCM C10	5-6	C8/C10 MG [> 45 % MG; > 45 % C10]	Abitec
Capmul® MCM C8	5-6	C8/C10 MG [68 % MG, 27 % DG, 3 % TG; > 95 % C8, 3 % C10]	Abitec
Captex® 355	1	C8/C10 TG	Abitec
Imwitor® 742	3-4	C8/C10 MG/DG/TG [45-55 % MG]	Sasol
Imwitor® 928	-	C12 MG/DG/TG of saturated FA [40% MG]	Sasol

Labrafac® CM 10	10	PEG C8/C10 glycerides [50 % C8, 50 % C10]	Gattefossé
Labrafacv Lipophile WL 1349	2	C8/C10 TG [50-80 % C8, 20-50 % C10]	Gattefossé
Miglyol® 810	-	C8/C10 TG [65-80 % C8, 20-35 % C10]	Sasol
Miglyol® 812	-	C8/C10 TG [50-65 % C8, 30-45 % C10]	Sasol
Miglyol® 818	-	C8/C10/C18:2 TG [45-65 % C8, 30-45 % C10, 2-5 % C18:2]	Sasol
Long chain glycerides			
Cithrol® GMS 40	3-5	C18 MG and DG	Croda
Maisine® 35-1	4	C18:1/ C18/ C16 MG [> 50 % C18, 10-35 % C18:1, < 6 % C18, 4-20 % C16]	Gattefossé
Myverol® 18-92	3.7	Distilled sunflower oil MG [7 % C16, 4.5 % C18, 18.7 % C18:1, 67.5 % C18:2]	Eastman
Peceol®	3.3	C18:1/ C18:2/ C18/ C16 MG [> 60 % C18:1, < 35 % C18:2, < 6 % C18, < 12 % C16]	Gattefossé
Plurol oleique® CC 497	6	Polyglyceryl-3 dioleate	Gattefossé
Plurol® Diisostearate	4.5	Polyglyceryl-3 diisostearate	Gattefossé
Soybean oil	-	C18:1/C18:2 TG	Central Soya
Propylene glycol esters			
Capmul® PG-12	4-5	C12 ME of propylene glycol	Abitec
Capmul®PG-8	6-7	C8 ME of propylene glycol	Abitec
Capryol® 90	6	C8 ME of propylene glycol [> 90 % ME of C8]	Gattefossé
Capryol® PGMC 90	5	C8 ME of propylene glycol [> 60 % ME, > 90 % C8]	Gattefossé
Captex® 200	-	C8/C10 DE of propylene glycol	Abitec
Captex® 200 P	2	C8/C10 DE of propylene glycol	Abitec
Labrafac® PG	2	C8/C10 DE of propylene glycol	Gattefossé
Lauroglycol® 90	5	C12 ME of propylene glycol [> 90 % ME, > 95 % C12]	Gattefossé
Lauroglycol® FCC	4	C12 ME/DE of propylene glycol [45-70 % ME, 30- 55 % DE; > 95 % C12]	Gattefossé
Miglyol® 840	-	C8/C10 DE of propylene glycols	Sasol
PEG glycerides			
Labrafil® M 1944 CS	4	C18:1 PEG-6 glycerides [58-68 % C18:1, 22-32 % C18:2]	Gattefossé
Labrafil® M 2125 CS	4	C18:2 PEG-6 glycerides [24-34 % C18:1, 53-63 % C18:2]	Gattefossé
Labrafil® M 2130 CS	4	C12 PEG-6 glycerides	Gattefossé
Labrafil® WL 2609 BS	6	C18:2 PEG glycerides [24-34 % C18:1, 53-63 % C18:2]	Gattefossé
Tagat® TO	11.3	C18:1 PEG-25 TG	Evonik
Sorbitan esters			
Span® 20	9	C12 sorbitan ME	Croda
Span® 60	5	C18 sorbitan ME	Croda
Span® 80	4	C18:1 sorbitan ME	Croda
Tween ® 85	11	PEG-20 C18:1 sorbitan TE	Croda
Miscellaneo s			
Centrophase® 31	4	60 % liquid lecithin, 40 % soybean oil; molecular weight = 800	Central Soya
Cithrol® GMO 50	2.8	Glyceryl oleate: propylene glycol (90:10)	Croda

Table 7: Examples of the commonly used more hydrophilic amphiphiles in the formulation of SNEDDS (adapted from[24, 28, 82]).

Excipient name (former name)	HLB	Description	Supplier
Acconon® C-44	13-14	PEG-32 C12 glycerides	Abitec
Acconon® CC-6	12.5	PEG-6 C8/C10 glycerides	Abitec
Acconon® MC8-2	14-15	PEG-6 C8/C10 glycerides	Abitec
Gelucire® 44/14	14	PEG-32 C12 glycerides	Gattefossé
Gelucire® 50/13	13	PEG-32 C18/C16 glycerides	Gattefossé
Kolliphor® EL (Cremophor® EL)	13.5	PEG-35 castor oil	BASF
Kolliphor® HS 15 (Solutol® HS 15)	14-16	PEG-15 esters of 12-hydroxystearic acid	BASF
Kolliphor® P188 (Lutrol® F68)	29	Poloxamer 188	BASF
Kolliphor® RH 40 (Cremophore® RH40)	14-16	PEG-40 hydrogenated castor oil (C16/C18)	BASF
Kolliphor® TPGS	13.2	D-α-tocopheryl PEG-1000 succinate	BASF
Labrasol®	14	PEG-8 C8/C10 glycerides	Gattefossé
Tween® 20	16	PEG-20 C12 sorbitan ME	Croda
Tween® 60	15	PEG-20 C18 sorbitan ME	Croda
Tween® 80	15	PEG-20 C18:1 sorbitan ME	Croda

Therefore, supersaturable SEDDS were developed. They contain precipitation inhibitors in order to generate and maintain a metastable drug supersaturation state. Furthermore, they improve the toxicity/safety profile of the SEDDS by reducing the amounts of the used surfactants.[28,29,90,91] Antioxidants could be incorporated in the SEDDS to increase the shelf-life stability by protecting the unsaturated lipids or the PWSDs against oxidations.[20]

SEDDS can be formulated as liquid, semisolid or solid dosage forms.[21] The liquid and semisolid SEDDS are usually filled in soft or hard gelatin capsules while the solid ones are compressed into tablets or filled as freely flowable powders or pellets into hard gelatin capsules. Recently, several novel approaches and patented techniques have been evaluated for the formulation of the SNEDDS.[21,68] Examples are: self-emulsifying osmotic pumps[68], gastroretentive SEDDS[93], mucoadhesive SEDDS[94], eutectic SEDDS[95,96], self-emulsifying phospholipids suspension[97,98], self-emulsifying supersaturable systems[98], carbon nanotubes-based SEDDS[101], cationic SEDDS[102], polymeric SEDDS[103], self-emulsifying glasses[104, 105] and self-double emulsifying drug delivery systems (SDEDDS).[63,106]

Table 8: Examples of the miscellaneous excipients used in the formulation Snedds.[20,29,62,99,100,107,108]

Excipients class	Examples
Co-solvents	
Diethylene glycol monoethyl ether	Transcutol® HP, Transcutol® P
Organic solvents	Ethanol, Glycerin, Polypylene glycol, Polyethylene glycol
Precipitation inhibitors	
Water-soluble cellulosic polymers	Hydroxypropyl Methylcellulose (HPMC), Methylcellulose (MC), Hydroxypropyl Methylcellulose Phthalate (HPMCP), Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS), Sodium Carboxymethylcellulose (NaCMC)
Water-soluble Polyvinylpyrrolidone	Povidone (PVP)
Block co-polymers	Ploxamers (Pluronic® F68, Pluronic® F127)
Graft co-polymers	Soluplus®
Antioxidants	
Natural	α-Tocopherol, β-Carotene
Synthetic	Butylated Hydroxytoluene (BHT), Butylated Hydroxyanisole (BHA), *tert*-Butythydroquinone (TBHQ), Propyl Gallate (PG)

S-SNEDDS were formulated as pellets[112,113], conventional tablets[114], bilayer tablets[115], effervescent tablets[116], orodispersible tablets[117], capsules[118], tablet-loaded pulsatile capsules[119], osmotic pumps[68, 92], microparticles[120], nanoparticles[121], mouth dissolving films[122], beads[123], lipid matrices[124] and self-emulsifying glasses.[104,105] Several approaches were evaluated for the manufacture of the S-SNEDDS.[65,68,69,71,125] These approaches could be summarized into: (a) The use of solid or semisolid lipids, (b) Incorporation of polymeric excipients/amphiphiles, (c) Lyophilization, (d) Extrusion/spheronization, (e) Adsorption onto solid carrier, (f) Liquisolid technique, (g)Fluid bed coating.

REFERENCES

1. Lipinski, CA, et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.* Advanced Drug Delivery Reviews, 1997; 23(1-3): 3-25.
2. Lipinski, CA, et al., *Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings.* Advanced Drug Delivery Reviews, 2001; 46(1-3): 3-26.
3. Kim, C-K, and Park, J-S, *Solubility enhancers for oral drug delivery*. American Journal of Drug Delivery, 2004; 2(2): 113-130.

4. Singh, A, et al., *Oral formulation strategies to improve solubility of poorly water- soluble drugs.* Expert Opinion on Drug Delivery, 2011; 8(10): 1361-1378.
5. Lipinski, CA, *Drug-like properties and the causes of poor solubility and poor permeability.* Journal of Pharmacological and Toxicological Methods, 2000; 44(1): 235-249.
6. Amidon, G, et al., *A theoretical basis for a biopharmaceutic drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability.* Pharmaceutical Research, 1995; 12(3): 413-420.
7. Lennernäs, H, and Abrahamsson, B, *The biopharmaceutics classification system*, in John, BT, *et al.*, Editors, *Comprehensive medicinal chemistry II*. 2007, Elsevier: Oxford, 971-988.
8. Yu, L, et al., *Biopharmaceutics classification system: the scientific basis for biowaiver Extensions.* Pharmaceutical Research, 2002; 19(7): 921-925.
9. Pouton, CW, *Formulation of poorly water-soluble drugs for oral administration: Physicochemical and physiological issues and the lipid formulation classification system.* European Journal of Pharmaceutical Sciences, 2006; 29(3-4): 278-287.
10. Di, L, et al., *Bridging solubility between drug discovery and development.* Drug Discovery Today, 2012; 17(9–10): 486-495.
11. Di, L, et al., *Drug-like property concepts in pharmaceutical design.* Current Pharmaceutical Design, 2009; 15(19): 2184-2194.
12. Bergström, CA, et al., *Poorly soluble marketed drugs display solvation limited solubility.* Journal of Medicinal Chemistry, 2007; 50(23): 5858-5862.
13. Anuta, V, et al., *Biopharmaceutical profiling of new antitumor pyrazole derivative,* Molecules, 2014; 19(10): 16381-16401.
14. Kakran, M, et al., *Overcoming the challenge of poor drug solubility.* Pharmaceutical Engineering, 2012; 32(4): 1-7.
15. Williams, HD, et al., *Strategies to address low drug solubility in discovery and development.* Pharmacological Reviews, 2013; 65(1): 315-499.
16. Fahy, E, et al., *A comprehensive classification system for lipids.* Journal of Lipid Research, 2005; 46(5): 839-861.
17. Small, D, *A classification of biologic lipids based upon their interaction in aqueous systems.* Journal of the American Oil Chemists Society, 1968; 45(3): 108-119.
18. Hauss, DJ, et al., *Lipid-based delivery systems for improving the bioavailability and lymphatic transport of a poorly water-soluble LTB4 inhibitor.* Journal of Pharmaceutical

Sciences, 1998; 87(2): 164-169.

19. Pouton, CW, *Lipid formulations for oral administration of drugs: Non-emulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems*. European Journal of Pharmaceutical Sciences, 2000; 11: S93-S98.
20. Pouton, CW, and Porter, CJ, *Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies.* Advanced Drug Delivery Reviews, 2008; 60(6): 625-637.
21. Gupta, S, et al., *Formulation strategies to improve the bioavailability of poorly absorbed drugs with special emphasis on self-emulsifying systems.* ISRN Pharmaceutics, 2013; 2013: 848043.
22. Mu, H, et al., *Lipid-based formulations for oral administration of poorly water-soluble drugs.* International Journal of Pharmaceutics, 2013; 453(1): 215-224.
23. Anton, N, and Vandamme, TF, *Nano-emulsions and micro-emulsions: Clarifications of the critical differences.* Pharmaceutical Research, 2011; 28(5): 978-985.
24. Nanjwade, BK, et al., *Functions of lipids for enhancement of oral bioavailability of poorly water-soluble drugs.* Scientia Pharmaceutica, 2011; 79(4): 705-727.
25. Porter, CJ, et al., *Enhancing intestinal drug solubilisation using lipid-based delivery systems.* Advanced Drug Delivery Reviews, 2008; 60(6): 673-691.
26. Humberstone, AJ, and Charman, WN, *Lipid-based vehicles for the oral delivery of poorly water soluble drugs.* Advanced Drug Delivery Reviews, 1997; 25(1): 103- 128.
27. Porter, CJH, et al., *Lipids and lipid-based formulations: Optimizing the oral delivery of lipophilic drugs.* Nature Reviews Drug Discovery, 2007; 6(3): 231-248.
28. Rahman, MA, et al., *Role of excipients in successful development of self-emulsifying/microemulsifying drug delivery system (SEDDS/SMEDDS).* Drug Development and Industrial Pharmacy, 2013; 39(1): 1-19.
29. Song, WH, et al., *Enhanced dissolution of celecoxib by supersaturating self-emulsifying drug delivery system (S-SEDDS) formulation.* Archives of Pharmacal Research, 2013; 36(1): 69-78.
30. Borovicka, J, et al., *Regulation of gastric and pancreatic lipase secretion by CCK and cholinergic mechanisms in humans.* American Journal of Physiology-Gastrointestinal and Liver Physiology, 1997; 36(2): G374-G380.
31. N'Goma, JCB, et al., *Understanding the lipid-digestion processes in the GI tract before designing lipid-based drug-delivery systems.* Therapeutic Delivery, 2012; 3(1): 105- 124.
32. Michele G.Issa, Humberto G.Ferraz., Intrinsic dissolution as a tool for evaluating drug

solubility in accordance with the Biopharmaceutics classification system. Dissolution technologies, 2011; 6-13.

33. Lengsfeld, H, et al., *Physiology of gastrointestinal lipolysis and therapeutical use of lipases and digestive lipase inhibitors*, in, *Lipases and phospholipases in drug development*., Wiley-VCH Verlag GmbH & Co. KGaA: Weinheim, 2005; 195-229.
34. Carrière, F, et al., *Quantitative study of digestive enzyme secretion and gastrointestinal lipolysis in chronic pancreatitis.* Clinical Gastroenterology and Hepatology, 2005; 3(1): 28-38.
35. Carriere, F, et al., *Secretion and contribution to lipolysis of gastric and pancreatic lipases during a test meal in humans.* Gastroenterology, 1993; 105(3): 876-888.
36. Renou, C, et al., *Effects of lansoprazole on human gastric lipase secretion and intragastric lipolysis in healthy human volunteers.* Digestion, 2001; 63(4): 207-213.
37. Hamosh, M, et al., *Fat digestion in the newborn: characterization of lipase in gastric aspirates of premature and term infants.* Journal of Clinical Investigation, 1981; 67(3): 838-846.
38. Bezzine, S, et al., *Human pancreatic lipase: Colipase dependence and interfacial binding of lid domain mutants.* Biochemistry, 1999; 38(17): 5499-5510.
39. Dahim, M, and Brockman, H, *How colipase−fatty acid interactions mediate adsorption of pancreatic lipase to interfaces.* Biochemistry, 1998; 37(23): 8369-8377.
40. Hildebrand, P, et al., *Hydrolysis of dietary fat by pancreatic lipase stimulates cholecystokinin release.* Gastroenterology, 1998; 114(1): 123-129.
41. McLaughlin, J, et al., *Fatty acid chain length determines cholecystokinin secretion and effect on human gastric motility.* Gastroenterology, 1999; 116(1): 46-53.
42. Hunt, J, and Knox, M, *A relation between the chain length of fatty acids and the slowing of gastric emptying.* The Journal of Physiology, 1968; 194(2): 327-336.
43. Fernandez, S, et al., *Lipolysis of the semi-solid self-emulsifying excipient gelucire® 44/14 by digestive lipases.* Biochimica et Biophysica Acta (BBA) - Molecular and Cell Biology of Lipids, 2008; 1781(8): 367-375.
44. Shen.J and Burgess J.D. *In vitro* Dissolution testing strategies for nanoparticulate drug delivery systems: Recent development and challenges, Drug delivery and translational research, 2013; 13(5); 409-415.
45. Suparna Sacchit Bakhle, Jasmine Gev Avari., Development and characterization of solid self-emulsifying drug delivery system of cilnidipine. Chem. Pharm. Bull., 2015; 63: 408-417.

46. Hernell, O, et al., *Physical-chemical behavior of dietary and biliary lipids during intestinal digestion and absorption. 2. Phase analysis and aggregation states of luminal lipids during duodenal fat digestion in healthy adult human beings.* Biochemistry, 1990; 29(8): 2041-2056.
47. Sek, L, et al., *Evaluation of the in-vitro digestion profiles of long and medium chain glycerides and the phase behaviour of their lipolytic products.* Journal of Pharmacy and Pharmacology, 2002; 54(1): 29-41.
48. Kossena, GA, et al., *Probing drug solubilization patterns in the gastrointestinal tract after administration of lipid-based delivery systems: A phase diagram approach.* Journal of Pharmaceutical Sciences, 2004; 93(2): 332-348.
49. Kossena, GA, et al., *Influence of the intermediate digestion phases of common formulation lipids on the absorption of a poorly water-soluble drug.* Journal of Pharmaceutical Sciences, 2005; 94(3): 481-492.
50. Westergaard, H, and Dietschy, JM, *The mechanism whereby bile acid micelles increase the rate of fatty acid and cholesterol uptake into the intestinal mucosal cell.* Journal of Clinical Investigation, 1976; 58(1): 97-108.
51. Dulfer, WJ, et al., *Effect of fatty acids and the aqueous diffusion barrier on the uptake and transport of polychlorinated biphenyls in Caco-2 cells.* Journal of lipid research, 1996; 37(5): 950-961.
52. Thomson, ABR, et al., *Lipid absorptions passing through the unstirred layers, brush-border membrane, and beyond.* Canadian Journal of Physiology and Pharmacology, 1993; 71(8): 531-555.
53. Simmonds, WJ, *The role of micellar solubilization in lipid absorption.* Immunology and Cell Biology, 1972; 50(4): 403-421.
54. Shiau, Y, et al., *Acidic mucin layer facilitates micelle dissociation and fatty acid diffusion.* American Journal of Physiology - Gastrointestinal and Liver Physiology, 1990; 259(4 Part 1): G671-G675.
55. Nordskog, BK, et al., *An examination of the factors affecting intestinal lymphatic transport of dietary lipids.* Advanced Drug Delivery Reviews, 2001; 50(1-2): 21-44.
56. Porter, CJH, and Charman, WN, *Intestinal lymphatic drug transport: An update.* Advanced Drug Delivery Reviews, 2001; 50(1-2): 61-80.
57. Cater, NB, et al., *Comparison of the effects of medium-chain triacylglycerols, palm oil, and high oleic acid sunflower oil on plasma triacylglycerol fatty acids and lipid and lipoprotein concentrations in humans.* The American Journal of Clinical Nutrition, 1997;

65(1): 41-45.

58. Bergstedt, SE, et al., *A comparison of absorption of glycerol tristearate and glycerol trioleate by rat small intestine.* American Journal of Physiology - Gastrointestinal and Liver Physiology, 1990; 259(3): G386-G393.
59. Charman, WNA, and Stella, VJ, *Estimating the maximal potential for intestinal lymphatic transport of lipophilic drug molecules.* International Journal of Pharmaceutics, 1986; 34(1-2): 175-178.
60. Trevaskis, NL, et al., *An examination of the interplay between enterocyte-based metabolism and lymphatic drug transport in the rat.* Drug Metabolism and Disposition, 2006; 34(5): 729-733.
61. Pantaleo, G, et al., *Role of lymphoid organs in the pathogenesis of human immunodeficiency virus (HIV) infection.* Immunological Reviews, 1994; 140(1): 105- 130.
62. Strickley, RG, *Solubilizing excipients in oral and injectable formulations.*Pharmaceutical Research, 2004; 21(2): 201-230.
63. Qi, XL, et al., *Self-double-emulsifying drug delivery system (SDEDDS): A new way for oral delivery of drugs with high solubility and low permeability.* International Journal of Pharmaceutics, 2011; 409(1-2): 245-251.
64. Dokania, S, and Joshi, AK, *Self-microemulsifying drug delivery system (SMEDDS) – Challengesand road ahead.* Drug Delivery, 2014. DOI:10.3109/10717544.2014.896058
65. Niederquell, A, and Kuentz, M, *Proposal of stability categories for nano-dispersions obtained from pharmaceutical self-emulsifying formulations.* International Journal of Pharmaceutics, 2013; 446(1-2): 70-80.
66. Khan, AW, et al., *Potentials and challenges in self-nanoemulsifying drug delivery systems.* Expert Opinion on Drug Delivery, 2012; 9(10): 1305-1317.
67. Vonderscher, J, and Meinzer, A. *Rationale for the development of sandimmune neoral*. in *Transplantation proceedings*, 1994. Elsevier.
68. Singh, B, et al., *Recent advances in self-emulsifying drug delivery systems (SEDDS).*Critical Reviews™ in Therapeutic Drug Carrier Systems, 2014; 31(2): 121-185.
69. Kumar, A, et al., *Self emulsifying drug delivery system (SEDDS): Future aspects.* International Journal of Pharmacy and Pharmaceutical Sciences, 2010; 2(4): 7-13.
70. Mallikarjun, V, and Rajesh Babu, V, *Recent trends in development of solid-self emulsifying drug Delivery (S-SEDDS) systems: An overview*. International Research Journal of Pharmacy, 2011; 2(6): 18-22.

71. Tang, B, et al., *Development of solid self-emulsifying drug delivery systems: Preparation techniques and dosage forms.* Drug Discovery Today, 2008; 13(13-14): 606-612.
72. Gugulothu, D, et al., *Self-microemulsifiyng suppository formulation of beta-artemether.* AAPS Pharm Sci Tech, 2010; 11(3): 1179-1184.
73. Lee, S, et al., *Design and evaluation of prostaglandin E1 (PGE1) intraurethral liquid formulation employing self-microemulsifying drug delivery system (SMEDDS) for erectile dysfunction treatment.* Biological and Pharmaceutical Bulletin, 2008; 31(4): 668-672.
74. Lo, J-T, et al., *Self-emulsifying O/W formulations of paclitaxel prepared from mixed nonionic surfactants.* Journal of Pharmaceutical Sciences, 2010; 99(5): 2320-2332.
75. Chae, GS, et al., *Enhancement of the stability of BCNU using self-emulsifying drug deliver systems (SEDDS) and in vitro antitumor activity of self-emulsified BCNU- loaded PLGA water*. International Journal of Pharmaceutics, 2005; 301(1-2): 6-14.
76. El Maghraby, GM, *Self-microemulsifying and microemulsion systems for transdermal delivery of indomethacin: Effect of phase transition.* Colloids and Surfaces B-Biointerfaces, 2010; 75(2): 595-600.
77. Czajkowska-Kosnik, A, and Sznitowska, M, *Solubility of ocular therapeutic agents in self-emulsifying oils I. Self-emulsifying oils for ocular drug delivery: Solubility of indomethacin, aciclovir and hydrocortisone.* Acta Poloniae Pharmaceutica, 2009; 66(6): 709-713.
78. Reiss, H, *Entropy-induced dispersion of bulk liquids.* Journal of Colloid and Interface Science, 1975; 53(1): 61-70.
79. Wakerly, MG, et al., *Self-emulsification of vegetable oil-nonionic surfactant mixtures*, in Scamehorn, JF, Editor, *Phenomena in mixed surfactant systems*., American Chemical Society: Washington, 1986; 242-255.
80. Pouton, CW, *Self-emulsifying drug delivery systems: Assessment of the efficiency of emulsification.* International Journal of Pharmaceutics, 1985; 27(2-3): 335-348.
81. Pouton, CW, *Formulation of self-emulsifying drug delivery systems.* Advanced Drug Delivery Reviews, 1997; 25(1): 47-58.
82. Chen, XQ, et al., *Application of lipid-based formulations in drug discovery.* Journal of Medicinal Chemistry, 2012; 55(18): 7945-7956.
83. Jannin, V, et al., *Approaches for the development of solid and semi-solid lipid-based formulations.* Advanced Drug Delivery Reviews, 2008; 60(6): 734-746.
84. Cao, Y, et al., *Predictive relationships for the effects of triglyceride ester concentration and water uptake on solubility and partitioning of small molecules into lipid vehicles.*

Journal of Pharmaceutical Sciences, 2004; 93(11): 2768-2779.

85. Charman, WN, and Stella, VJ, *Transport of lipophilic molecules by the intestinal lymphatic system.* Advanced Drug Delivery Reviews, 1991; 7(1): 1-14.
86. Bandyopadhyay, S, et al., *Optimized self nano-emulsifying systems of ezetimibe with enhanced bioavailability potential using long chain and medium chain triglycerides.* Colloids and Surfaces B-Biointerfaces, 2012; 100: 50-61.
87. Caliph, SM, et al., *Effect of short-, medium-, and long-chain fatty acid-based vehicles on the absolute oral bioavailability and intestinal lymphatic transport of halofantrine and assessment of mass balance in lymph-cannulated and non-cannulated rats.* Journal of Pharmaceutical Sciences, 2000; 89(8): 1073-1084.
88. Beg, S, et al., *Development of solid self-nanoemulsifying granules (SSNEGs) of ondansetron hydrochloride with enhanced bioavailability potential.* Colloids and Surfaces B-Biointerfaces, 2013; 101: 414-423.
89. Thomas, N, et al., *Influence of lipid composition and drug load on the in vitro performance of self-nanoemulsifying drug delivery systems.* Journal of Pharmaceutical Sciences, 2012; 101(5): 1721-1731.
90. Patel, V, et al., *Self emulsifying drug delivery system: A conventional and alternative appproach to improve oral bioavailability of lipophilic drugs.* International Journal of Drug Development and Research, 2010; 2(4): 859-870.
91. Kohli, K, et al., *Self-emulsifying drug delivery systems: an approach to enhance oral bioavailability.* Drug Discovery Today, 2010; 15(21-22): 958-965.
92. Bagul, N, et al., *Design and development of solid self emulsifying osmotic delivery system of nifedipine.* Archives of Pharmacy Practice, 2012; 3(2): 128-135.
93. Setthacheewakul, S, et al., *Controlled release of oral tetrahydrocurcumin from a novel self-emulsifying floating drug delivery system (SEFDDS).* AAPS Pharm SciTech, 2011; 12(1): 152-164.
94. Vipul Rokad, Chirag Nagda, Dhruti Nagda., Design and evaluation of solid self-emulsifying drug delivery system of Rosuvastatin calcium. JYP, 2014; 6(3): 37-46.
95. Madhvi K, Shikha A, Suresh B., Formulation and *in vitro* characterization solid self-emulsifying drug delivery system of Ramipril prepared by adsorption technique. *Int J Curr Pharm Res,* 2016; 8(1): 40-45.
96. Nazzal, S, et al., *Preparation and in vitro characterization of a eutectic based semisolid self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone: Mechanism and progress of emulsion formation.* International Journal of Pharmaceutics, 2002; 235(1- 2):

247-265.

97. Ruan, JH, et al., *Preparation and evaluation of self-nanoemulsified drug delivery systems (SNEDDSs) of matrine based on drug-phospholipid complex technique.* International Journal of Pharmaceutics, 2010; 386(1-2): 282-290.
98. Zhou, H, et al., *A new strategy for enhancing the oral bioavailability of drugs with poor water-solubility and low liposolubility based on phospholipid complex and supersaturated SEDDS.* Plos One, 2013; 8(12).
99. Gao, P, et al., *Enhanced oral bioavailability of a poorly water soluble drug PNU-91325 by supersaturatable formulations.* Drug Development and Industrial Pharmacy, 2004; 30(2): 221-229.
100. Wei, Y, et al., *Enhanced oral bioavailability of silybin by a supersaturatable self-emulsifying drug delivery system (S-SEDDS).* Colloids and Surfaces A: Physicochemical and Engineering Aspects, 2012; 396: 22-28.
101. Vasanti Suvarna, Utkarsha Pagdhare, Anila Kadu, Manisha Oza., Development and characterization of solid self-emulsifying drug delivery system containing Nateglinide. Asian journal of Pharmaceutics, 2017; 11(10): 27-36.
102. Gershanik, T, et al., *Interaction of a self-emulsifying lipid drug delivery system with the everted rat intestinal mucosa as a function of droplet size and surface charge.* Pharmaceutical Research, 1998; 15(6): 863-869.
103. Suparna Sacchit Bakhle, Jasmine Gev Avari., Development and characterization of solid self-emulsifying drug delivery system of cilnidipine. Chem. Pharm. Bull., 2015; 63: 408-417.
104. Madhvi K, Shikha A, Suresh B., Formulation and *in vitro* characterization solid self-emulsifying drug delivery system of Ramipril prepared by adsorption technique. *Int J Curr Pharm Res.*, 2016; 8(1): 40-45.
105. Myers, SL, and Shively, ML, *Preparation and characterization of emulsifiable glasses: Oil-in-water and water-in-oil-in-water emulsions.* Journal of Colloid and Interface Science, 1992; 149(1): 271-278.
106. Lv, L-Z, et al., *Enhanced absorption of hydroxysafflor yellow A using a self-double-emulsifying drug delivery system: In vitro and in vivo studies.* International Journal of Nanomedicine, 2012; 7: 4099.
107. Atef, E, and Belmonte, AA, *Formulation and in vitro and in vivo characterization of a phenytoin self-emulsifying drug delivery system (SEDDS).* European Journal of Pharmaceutical Sciences, 2008; 35(4): 257-263.

108. R.Neslihan Gursoy, Simson Benita., Self-emulsifying drug delivery systems (SEDDS) for improved oral drug delivery of lipophilic drugs. Biomedicine & Pharmacotherapy, 2004; 58: 173-182.
109. Zhu, X, et al., *Target release rate of antioxidants to extend induction period of lipid oxidation.* Food Research International, 2012; 47(1): 1-5.
110. Bowtle, WJ, *Materials, process, and manufacturing considerations for lipid-based hard-capsule formats*, in Hauss, DJ, Editor, *Oral lipid-based formulations: Enhancing the bioavailability of poorly water-soluble drugs*., Informa Healthcare: New York., 2007; 97-106.
111. Serajuddin, ATM, et al., *Water migration from soft gelatin capsule shell to fill material and its effect on drug solubility.* Journal of Pharmaceutical Sciences, 1986; 75(1): 62- 64.
112. Abdalla, A, and Mäder, K, *Preparation and characterization of a self-emulsifying pellet formulation.* European Journal of Pharmaceutics and Biopharmaceutics, 2007; 66(2): 220-226.
113. Lei, Y, et al., *Solid self-nanoemulsifying cyclosporin A pellets prepared by fluid-bed coating: Preparation, characterization and in vitro redispersibility.* International Journal of Nanomedicine, 2011; 6: 795-805.
114. Swamy, NGN, and Shiny, EK, *Formulation and evaluation of telmisartan liquisolid tablets.* Rajiv Gandhi University of Health Sciences Journal of Pharmaceutical Sciences, 2013; 3(3): 49-57.
115. Sohn, Y, et al., *Development of self-microemulsifying bilayer tablets for pH- independent fast release of candesartan cilexetil.* Pharmazie, 2012; 67(11): 917-924.
116. Soliman, KA, et al., *Formulation of risperidone as self-nanoemulsifying drug delivery system in form of effervescent tablets.* Journal of Dispersion Science and Technology, 2012; 33(8): 1127-1133.
117. Zidan, AS, et al., *Taste-masked orodispersible tablets of cyclosporine self- nanoemulsion lyophilized with dry silica.* Pharmaceutical Development and Technology, 2014. DOI:10.3109/10837450.2014.908307:
118. Agarwal, V, et al., *Powdered self-emulsified lipid formulations of meloxicam as solid dosage forms for oral administration.* Drug Development and Industrial Pharmacy, 2013; 39(11): 1681-1689.
119. Huang, Y, et al., *A novel plug-controlled colon-specific pulsatile capsule with tablet of curcumin-loaded SMEDDS.* Carbohydrate Polymers, 2013; 92(2): 2218-2223.
120. Bremmell, KE, et al., *Tableting lipid-based formulations for oral drug delivery: A case*

study with silica nanoparticle–lipid–mannitol hybrid microparticles. Journal of Pharmaceutical Sciences, 2013; 102(2): 684-693.

121. Attama, AA, and Nkemnele, MO, *In vitro evaluation of drug release from self micro-emulsifying drug delivery systems using a biodegradable homolipid from Capra hircus.* International Journal of Pharmaceutics, 2005; 304(1-2): 4-10.
122. Xiao, L, et al., *A new self-microemulsifying mouth dissolving film to improve the oral bioavailability of poorly water soluble drugs.* Drug Development and Industrial Pharmacy, 2013; 39(9): 1284-1290.
123. Patil, P, and Paradkar, A, *Porous polystyrene beads as carriers for self-emulsifying system containing loratadine.* AAPS Pharm Sci Tech, 2006; 7(1): E1-E7.
124. R.Neslihan Gursoy, Simson Benita., Self-emulsifying drug delivery systems (SEDDS) for improved oral drug delivery of lipophilic drugs. Biomedicine & Pharmacotherapy, 2004; 58: 173-182.
125. Tan, A, et al., *Transforming lipid-based oral drug delivery systems into solid dosage forms: An overview of solid carriers, physicochemical properties, and biopharmaceutical performance.* Pharmaceutical Research, 2013; 30(12): 2993-3017.