AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: http://www.ajptr.com/

Review on Self Nanoemulsifying Drug Delivery System

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ABSTRACT

Self nanoemulsifying drug delivery (SNEDDS) is used for drugs which exhibit low water solubility. Dissolution is the rate limiting factor for these drugs. SNEDDS are capable of improving the bioavailability substantially of such drugs. They are formulated by utilizing an oil phase, surfactant and a co-surfactant. This formulation forms nano emulsion (O/W type) on contact with aqueous body fluids i.e gastric juices when administered orally. Solid SNEDDS (s-SNEDDS) can also be formulated in the form of tablet which shows greater advantages. With recent and potential future developments, this technology will continue to enable novel applications in drug delivery and overcome limitations associated with the delivery of poorly water soluble drugs, mainly those belonging to BCS class-II and class-IV.

Keywords: Self nanoemulsifying drug delivery system (SNEDDS), oil phase, surfactants, co-surfactants, Pseudo ternary phase diagrams.

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Received 12 April 2014, Accepted 26 April 2014

Please cite this article in press as: Amrutkar C *et al* Review on Self Nanoemulsifying Drug Delivery System. American Journal of PharmTech Research 2014.

INTRODUCTION

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which lead to poor oral bioavailability, high intra and inter subject variability and lack of dose proportionality[1]. Efforts are ongoing to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy[2]. Self emulsifying drug delivery systems have been shown to be successful in improving the oral bioavailability of poorly water soluble and lipophilic drugs [3].

Self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation which is mixture of oils and surfactants, ideally isotropic, and sometimes containing co-solvants, which emulsify spontaneously to produce fine oil in water emulsion when introduced into aqueous phase under gentle agitatio[4,5] Self-nanoemulsifying (SNEDDS), self microemulsifying (SMEDDS) and self-emulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly water-soluble drugs [6-8]

Self nano-emulsifying drug delivery systems

These systems have a unique property, they are able to self-emulsify rapidly in gastro-intestinal fluids and under the gentle agitation provided by the motion of the gastro-intestinal tract and they form fine O/W emulsions. These fine O/W emulsions produce small droplets of oil dispersed in the gastro-intestinal fluids that provide large interfacial area increasing the activity of pancreatic lipase to hydrolyze triglycerides and, thereby, promote a faster release of the drug and/or formation of mixed micelles of the bile salts containing the drug.[10]

Furthermore, in most cases the surfactant used for such formulations increases the bioavailability of the drug by activation of different mechanisms, maintaining the drug in solution and, thus, avoiding the dissolution step from the crystalline state and enhancing intestinal epithelial permeability at the same time. Moreover, the oil droplets lead to a faster and more uniform distribution of the drug in the gastrointestinal tract, minimizing the irritation due to contact between the drug and the gut wall. In addition, lipids affect the oral bioavailability of drugs by exerting their effect through several mechanisms, including protection of the drug from enzymatic or chemical degradation in the oil droplets and activation of lipoproteins promoting the lymphatic transport of lipophilic drugs. These systems may then be incorporated into capsules directly, or transformed into granules, pellets, and powders for dry filled capsules as well as tablet

preparations. The latter option is possible by innovative adaptations of conventional equipment with relative ease and process simplicity, using methods like melt granulation, adsorption on a solid support, spray drying, spray cooling, melt- extrusion/spheronization, and supercritical fluid based methods.[9, 10]

In Self Nanoemulsifying drug delivery systems:

Oil droplet size is: <100nm

Appearance is optically clear

Required HLB value is >12

FORMULATION COMPONENTS AND CONSIDERATIONS:

Successful formulation of SNEDDS depends on the through understanding of the spontaneous nano emulsification process and also on the physicochemical and biological properties of the components used for the fabrication of SNEDDS. The factors influencing the phenomenon of self nanoemulsification are:

1. The physicochemical nature and concentration of oily phase, surfactant and co-emulsifier or co surfactant or solubilizer (if utilized);
2. The ratio of the components, especially oil-to surfactant ratio;
3. The temperature and pH of the aqueous phase where nanoemulsification would occur;
4. Physicochemical properties of the drug, such as hydrophilicity/lipophilicity, pKa and polarity.

These factors should receive attention while formulating SNEDDS. In addition, the acceptability of the SNEDDS components for the desired route of administration is also very important while formulating SNEDDS. [11]

Advantages of SEDDS

Improvement in oral bioavailability:

The ability of SMEDDS to present the drug in git in solubilised form (globule size between 1-100nm) and subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability. E.g. In case of Halofantrine approximately 6-8 fold increase in bioavailability of drug was reported in comparison to tablet formulation [12].

Ease of manufacture and scale-up:

Ease of manufacture and scale-up is one of the most important advantage that makes SMEDDS unique when compared to other drug delivery systems like solid dispersions, liposomes, nanoparticles etc., dealing with improvement of bioavailability. SMEDDS requires very simple

and economical manufacturing facilities like simple mixer, agitators and volumetric liquid filing equipment for large scale manufacturing. This explains the interest of industry in the SMEDDS.

Reduction in inter-subject and intra-subject variability and food effects.

There are various drugs which show large in inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is a major factor affecting the therapeutic performance of the drug in the body. SMEDDS are a remedy for such a drug. Several research paper specifying that, the performance of SMEDDS is independent of food and, SMEDDS offer a reproducibility of plasma profile are available [13].

Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT:

One unique property that makes SMEDDS superior as compared to other drug delivery systems is their ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors and their ability to offer protection from enzymatic hydrolysis [14].

No influence of lipid digestion process:

Unlike the other lipid-based drug delivery systems, the performance of SMEDDS is not influence by the lipolysis, emulsification by the bile salts, action of pancreatic lipases and mixed micelle formation. SMEDDS are not necessary digested before the drug is absorbed as they present the drug in micro-emulsified form which can easily penetrate the mucin and water unstirred layer [15].

Increased drug loading capacity:

SMEDDS also provide the advantage of increased drug loading capacity when compared with conventional lipid solution as the solubility of poorly water soluble drugs with intermediate partition coefficient(2<log p>4) are typically low in natural lipids and much greater in amphilic surfactants, cosurfactants and cosolvents.

Sterilizable:

SNEDDS formulation can be sterilized; therefore they can be given parenterally with i.v. fluids [16].

COMPONENTS IN SELF- NANOEMULSIFYING DRUG DELIVERY SYSTEM:

1. Active Pharmaceutical Ingredient
2. Oil Phase
3. Surfactant
4. Cosurfactant

Oils:

The oil represents one of the most important excipients in the SEDDS formulation not only because it can solubilize marked amounts of the lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride [20-23]. Both long and medium chain triglyceride oils with different degrees of saturation have been used for the design of self-emulsifying formulations. Further more, edible oils which could represent the logical and preferred lipid excipients choice for the development of SEDDS are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs. Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties[17,18,19]. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion. Novel semi-synthetic medium chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium chain triglyceride oils in the SEDDS [18, 22]

Table 1: List of oils in Self-Emulsifying formulation [41, 42, 43, 44]

Category	**Natural and Semi synthetic oils**	
Hydrogenated vegetable oils	Sunflower oil, Castor oil, corn oil, Olive oil, Peanut oil, Copttonseed oil, Canola oil, Repeseed oil, Coconut oil, Soyabean oil ,Paim oil, Palm Kernel oil, Cocoa butter, Lard, Tallow	
Category	**Synthetic oils/Lipids**	
Mono-,Di- and Triglycerides	**Excipient Chemical Name**	**Trade Name(Supplier)**
	Glyceryl triacetate(triacetin)	Captex 500 P(Abitec Co) Triacetin(Sigma-Aldrich)
	Glyceryl mono-,ditribehenate	Compritol 888 ATO(Gattefosse)
	Glyceryl tribehenate	Syncrowax HR-C (Croda) Tribehenin (Sigma-Aldrich)
	Glyceryl tributyrate	Tributyrin (Sigma-Aldrich)
	Glyceryl mono and dicaprate	Capmul MCM C-10(Abitec CO)
	Glyceryl tricaprate (tricaprin)	Captex 1000 (Abitec CO) Tricaprin (Sigma-Aldrich)
	Glyceryl mono and dicaprylate	Capmul MCM C-8(Abitec CO) Imwitor 742 (Sasol)
	Glyceryl tricaprylate (tricaprylin)	Captex 8000 (Abitec CO) Neobee 895 (Stepan)
	Glyceryl mono and dicaprylate/caprate	Capmul MCM (Abitec CO)Imwitor 742 (Sasol)

Mono-,Di-,and Triglycerides	Glyceryl tricaprylate /caprate (medium chain triglycerides)	Migloyl 810(Sasol) Neobee 1053 (Stepan) Captex 300,355 (Abitec CO) Labrafac CC(Gattefosse)
	Glyceryl tricaprylate/caprate/laurate	Captex 350 (Abitec co)
	Glyceryl tricaprylate/caprate/linoleate	Captex 810D(Abitec CO
	Glyceryl monolaureate	Stepan GML(Stepan)
	Glyceryl monolinoleate	Maisine 35-1 (Gatterfosse)
	Glyceryl monoleate	Capmul GMO (Abitec co) Peceol (Gatterfosse)
	Glyceryl mono and dioleate	Capmul GMO-50 (Abitec co) Capmul GMO-K (Abitec co)
	Glyceryl mono-,di-,tristearate	Imwitor 900()Sasol
Polyglycerol Fatty Acid Esters	Polyglycerol-3-oleate	Caprol 3GO (Abitec co)
	Polyglycerol-3 dioleate	Plurol oleique CC497 (Abitec co)
	Polyglycerol-3 stearate	Caprol 3Gs (Abitec co)
Mixtures of Mono.Di, and Trigiycerides With fatty acid Esters of Polyethylene glycols	PEG-40 Hydrogenated castor oil	Cremophor RH 40(BASF)
	PEG-35 castor oil(polyoxyl 35 castor oil,USP/NF)	Cremophor EL (BASF) Etocas 35 NF (croda)
	PEG-6 glyceryl linoleate	Labrafil M 2125 CS (Gattefosse)

Surfactants:

Several compounds exhibiting surfactant properties may be employed for the design of self-emulsifying systems, the most widely recommended ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB). The commonly used emulsifiers are various solid or liquid ethoxylated polyglycolyzed glycerides and Polysorbate 80 (Tween 80). Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactants [17, 19, 25, 26]. However, these excipients have a limited self-emulsification capacity.

Non-ionic surfactants are less toxic than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen[25]. Usually the surfactant concentration ranges between 30 and 60% w/w in order to form stable SEDDS. It is very important to determine the surfactant concentration properly as large amounts of surfactants may cause GI irritation. The surfactant involved in the formulation of SEDDS should have a relatively high HLB (Table 4) and hydrophilicity so that immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media (good self-emulsifying performance) can be achieved. For an effective absorption, the precipitation of the drug compound within the GI lumen should be

prevented and the drug should be kept solubilized for a prolonged period of time at the site of absorption. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. The lipid mixtures with higher surfactant and co-surfactant/oil ratios lead to the formation of SNEDDS There is a relationship between the droplet size and the concentration of the surfactant being used. In some cases, increasing the surfactant concentration could lead to droplets with smaller mean droplet size such as in the case of a mixture of saturated C8-C10 polyglycolized glycerides (Labrafac CM-10). This could be explained by the stabilization of the oil droplets as a result of the localization of the surfactant molecules at the oil-water interface[30]. On the other hand, in some cases the mean droplet size may increase with increasing surfactant concentrations [31, 32]. This phenomenon could be attributed to the interfacial disruption elicited by enhanced water penetration into the oil droplets mediated by the increased surfactant concentration and leading to ejection of oil droplets into the aqueous phase.

Table 2: Emulsifiers used in SEDDS/SMEDDS formulations with their HLB values [41, 45]

Chemical Name	HLB*	Commercial/Brand Name
PEG-4 lauryl ether	9.7	Brij-30
PEG-6 corn oil	4	Labrafil M2125 CS
PEG-6 apricot kernel oil	4	Labrafil M1944 CS
PEG-8 caprylic/capric glycerides	14	Labrasol
PEG-8 caprylic/capric glycerides	>10	Labrafac CM 10
Polyoxyethylene-polyoxypropylene copolymer	18-23	Pluronic F 127
PEG-8 corn oil	6-7	Labrafil WL 2609 BS
L-a- phosphatidylcholine	4-9	Lecithin
PEG-20 sorbitan monooleate	15	Tween 80
PEG-20 sorbitan trioleate	11	Tween 85
PEG-20 sorbitan monolaurate	17	Tween 20
PEG-20 sorbitan tristearate	11	Tween 65
PEG-25 hydrogenated castor oil	11	Simusol 1292 Cerex ELS 250
PEG-25 trioleate	11	Tagat TO
PEG-35 castor oil	12-14	Cremophor-EL, Cremophor-ELP
PEG-40 hydrogenated castor oil	13	Cremophor RH 40
Sorbitan monooleate	4.3	Span 80
Glyceryl monoleate	3-4	Peceol
Ethoxylated castor oil	12-15	Emulphor EI-620

Co-surfactants

The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants. Organic solvents such as, ethanol, propylene glycol, and

polyethylene glycol are suitable for oral delivery, and they enable the dissolution of large quantities of either the hydrophilic surfactant or the drug in the lipid base. These solvents can even act as co-surfactants in microemulsion systems. On the other hand, alcohols and other volatile co-solvents have the disadvantage of evaporating into the shells of the soft gelatin, or hard, sealed gelatin capsules in conventional SEDDS leading to drug precipitation [22]. Thus, alcohol-free formulations have been designed, but their lipophilic drug dissolution ability may be limited. There are at least three reasons why cosolvents have been included in lipid-based formulations. More commonly it has been assumed that cosolvents could be included to increase the solvent capacity of the formulation for drugs which dissolve freely in cosolvents. However, to enhance the solvent capacity significantly the cosolvent must be present at high concentration and this is associated with the risk of drug precipitation when the formulation is dispersed in water cosolvents loose their solvent capacity quickly following dilution. A third reason for inclusion of cosolvents is to aid dispersion of systems which contain a high proportion of water-soluble surfactants. There are practical limits on the concentrations of cosolvents which can be used, governed by issues of immiscibility with oil components and also possible incompatibilities of low molecular weight cosolvents with capsule shells.

Table 3. list of cosurfactant used in SNEDDS [41, 45, 46]

Chemical Name	HLB	Commercial/Brand
Sodium Lauryl Sulfate	40	SLS
Poloxamer 188	29	Lutrol F 68
Diethylene glycol monoethyl ether	-	Carbitol
Methyl-oxirane polymer	12-18	Pluronic L 64
Block polymer of ethylene	12-18	Pluronic L44
Glyceryl caprylate	5-6	Capmul MCM-C8
Diethylene glycol mono ethyl	-	Transcutol P
Propylene glycol monolaurate	5	Lauroglycol 90
Polyglycerol-6 dioleate	6	Plurol Oleique
Propylene glycol monolaurate	4	Lauroglycol FCC
Sorbitan monooleate	4.3	Span 80
Caprylic/capric glycerides	56	Akoline MCM
PEG-6 apricot Kerneloil	4	Labrafil 1944

INACTIVE INGREDIENTS DATABASE

Table 4. USFDA-CDER Inactive Ingredient Database (IID) [33]

Sr. No.	Lipidic Solvents	Chemical Name	Maximum Potency
1.	Migloyl 812	Caprylic/ Capric triglyceride	USFDA IID, oral NR
2.	Lecithin	Lecithin, Hydrogenated Soya –	USFDA IID, oral capsule

		lecithin	263 mg
3.	Phosal 50 PG	Lecithin, egg lecithin, soyalecithin	USFDA IID, 250 mg
4.	12HSA-E 015 (Solutol HS 15)	Polyethylene glycol (660)-12-Hydroxysterate	USFDA IID, oral 153.9 mg
5.	Labrafac	Propylene glycol Dicaprylate/ dicaprate	USFDA IID, oral 10%
6.	Tetraglycol	Corn triglycerides	USFDA IID, oral 344 mg
	Alcohols	**Chemical Name**	**Maximum Potency**
1.	Benzyl alcohol	Benzyl alcohol	USFDA IID, oral 15 mg
2.	IPA	Isopropyl alcohol	USFDA IID, oral 300 mg
	Surfactants	**Chemical Name**	**Maximum Potency**
1.	Cremophore ELP	Polyoxyl 35 castor oil	USFDA IID, oral 600 mg
2.	Cremophore RH 40	Polyoxyl 40 hydrogenated castor oil	USFDA IID, oral 400 mg
3.	Solutol HS 15	PEG Sorbiton Monooleate	USFDA IID, oral 153.9 mg
4.	HCO 60	Hydrogenated castor oil	USFDA ID, oral 20%
5.	Tween 20	Polyoxyethylene Sorbiton fatty acid esters	USFDA IID, oral 56 mg
6.	Tween 40	Polysorbate 40	USFDA IID, oral 5%
7.	Tween 80	Polysorbate 80	USFDA IID, oral 418.3 mg
8.	Span 20	Sorbiton monolaurate	USFDA IID, oral 83.2 mg
9.	Span 80	Sorbiton monoleate	USFDA IID, oral 153.9 mg
10.	Myrj 45	Polyoxyl 8 stearate	USFDA IID, oral 2.5%
	Cosurfactants	**Chemical Name**	**Maximum Potency**
1.	Capryol 90	Propylene glycol caprylate	USFDA IID, oral 20%
2.	PEG 200	Polyethylene Glycol 200	USFDA IID, oral 20%
3.	PEG 300	Polyethylene Glycol 300	USFDA IID, oral 156 mg
4.	PEG 400	Polyethylene Glycol 400	USFDA IID, oral 960 mg
5.	PG	Propylene Glycol	USFDA IID, oral 148.1 mg
6.	PEG 4000	Polyethylene Glycol 4000	USFDA IID, oral 454 mg
7.	PEG 6000	Polyethylene Glycol 6000	USFDA IID, oral 450 mg

Pseudo ternary Phase Diagram

Pseudoternary phase diagram is used to map optimum concentration range of excipients according to the resulting droplet size following self emulsification, in vitro cell toxicity, stability upon dilution and viscosity. It is a good tool for optimizing SNEDDS composition. The phase behavior of simple microemulsion system consisting of oil, water and surfactant/co-surfactant mixture can be studied with the aid of pseudoternary phase diagram in which each corner of diagram represents 100% of that particular component. Phase diagram are useful tool to determine the number and types of phased, the %wt of each phase and the composition of each phase at a given temperature and composition of the system these diagram are three dimensional but are illustrated in two dimensions for ease of drawing and interpretation. Constructing phase diagram is time consuming, particularly when the aim is to accurately delineate a phase

boundary, as the phase boundry is approached. The procedure most often employed is to prepare a series of (pseudo) binary compositions and titrate with the third component, evaluating the mixture after each addition.

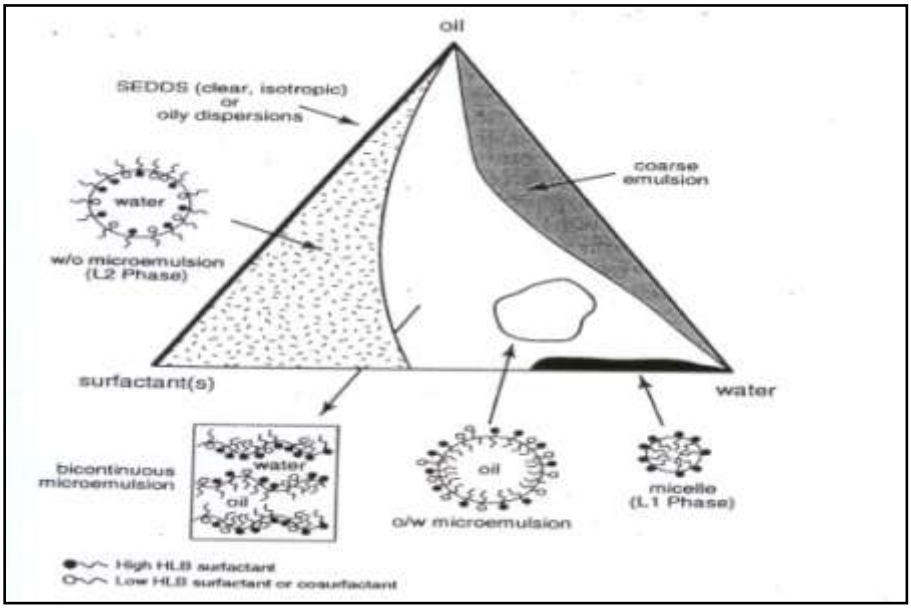

Figure 1. Pseudoternary phase diagram.

Interpretation of Pseudoternary phase diagram

These diagrams are three-dimensional but are illustrated in two-dimensions for ease of drawing and interpretation. In a ternary diagram the relative percentage (normally weight %) of three components are represented by **A, B** and **C**. The only requirement is that the three components have to sum to 100%. If they don't, you have to normalize them to 100% [34].

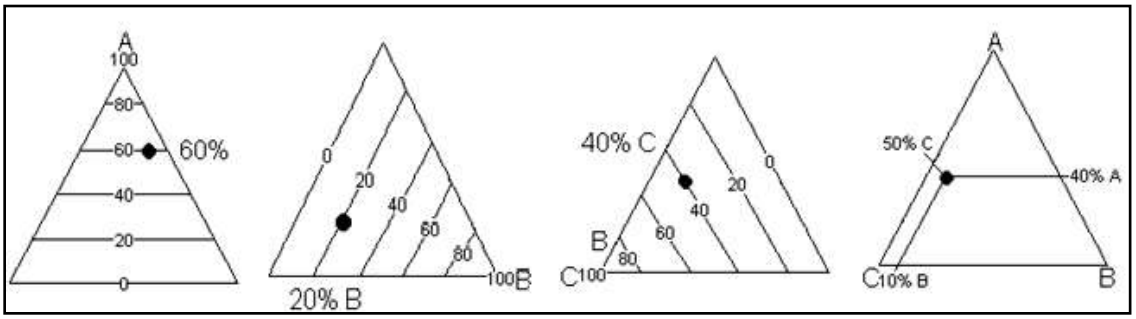

Figure 2. Interpretation of Pseudoternary phase diagram

CHARACTERIZATION OF SNEDDS

1. **Thermodynamic stability studies**

The physical stability of a lipid –based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only

formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug [37, 40]

i. Heating cooling cycle:

Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

ii. Centrifugation:

Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

iii. Freeze thaw cycle:

Those formulations pass this test show good stability with no phase separation, creaming, or cracking.

2. Self-Emulsification Time

The efficiency of self-emulsification is assessed using dissolution apparatus. 1ml SEDDS was dissolved in 250ml of water at 37±0.5◦C. Gentle agitation was provided by paddle rotating at 60RPM. SEDDS was assessed visually according the rate of emulsification and the final appearance of the emulsion. Time was noted in triplicates standard. Also any precipitation was observed visually [35, 39].

3. Dispersibility test

The efficiency of self-emulsification of oral nano emulsion is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation was added to 500 ml of water at 37 ± 0.5ıC. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The in vitro performance of the formulations is visually assessed using the following grading system [35]

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that formed within 2 minutes

Grade D: Dull, grayish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SNEDDS formulation.

4. Robustness to dilution

Formulations were subjected to 50,100,250 fold dilution with enzyme free simulated gastric fluid pH 1.2; enzyme free simulated intestinal fluid pH 6.8 and distilled water. The resultant diluted emulsions were observed for any physical changes like coalescence of droplets, precipitation or phase separation after 24 hrs [36]

5. Droplet size analysis and Particle size measurements

The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zeta sizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water [36]

6. Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SNEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids [39].

7. Refractive index and Percentage Transmittance

Refractive index and percent transmittance proves the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and it compare with water (1.333). The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance > 99 percent, then formulation have transparent nature [39].

8. Measurement of Polydispersity index

(PDI) is measure of droplet size homogeneity and it varies from 0.0 to 1.0. Polydispersity is the ratio of standard deviation to mean droplet size in the formulation. The higher the polydispersity, the lower the uniformity of the droplet size in the formulation. The closer to zero the polydispersity value the more homogenous are the droplets [39].

9. Cloud point measurement

The optimized SNEDDS formulations were diluted with distilled water in the ratio of 1:250. The diluted samples were placed in a water bath and its temperature was increased gradually.

Cloud point was spectrophotmetrically determined as the temperature at which there was a sudden appearance of cloudiness [38, 39].

10. Scanning Electron Microscope study:

Morphological examination of surface of Neusilin US2 and formulation adsorbed on Neusilin US2 was carried out using a scanning electron microscope. Particles were vacuum dried and coated with thin gold-palladium layer and observed microscopically at an accelerating voltage of 5.0 kV [39].

11. In Vitro Diffusion study

In vitro diffusion studies is performed for all the formulations developed, using a dialysis technique. The dialyzing medium is phosphate buffer pH 6.8. One end of pretreated cellulose dialysis tubing (7 cm in length) is tied with thread, and then 1 ml of self nano-emulsifying formulation is placed in it along with 0.5 ml of dialyzing medium. The other end of the tubing is also secured with thread and is allowed to rotate freely in 200 ml of dialyzing medium and stirred continuously at 100 rpm with magnetic bead on magnetic plate at 37°C. Aliquots of 1 ml are removed at different time intervals and diluted further. Volume of aliquots is replaced with fresh dialyzing medium each time. These samples are analyzed quantitatively for drug dialyzed across the membrane at corresponding time by using UV-visible spectrophotometer[38, 39]

12. Drug content determination

Drug from pre-weighed SNEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.

Biopharmaceutical Aspects

Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number of potential mechanisms including:

- Alterations (reduction) in gastric transit, thereby slowing delivery to the absorption site and increasing the time available for dissolution.
- Increases effective lumenal drug solubility. The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.

- Stimulation of intestinal lymphatic transport. For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly, or indirectly *via* a reduction in first-pass metabolism.
- Changes in the biochemical barrier function of the GI tract. It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p-glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.
- Changes in the physical barrier function of the GI tract. Various combinations of lipids, lipid digestion products and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs[40].

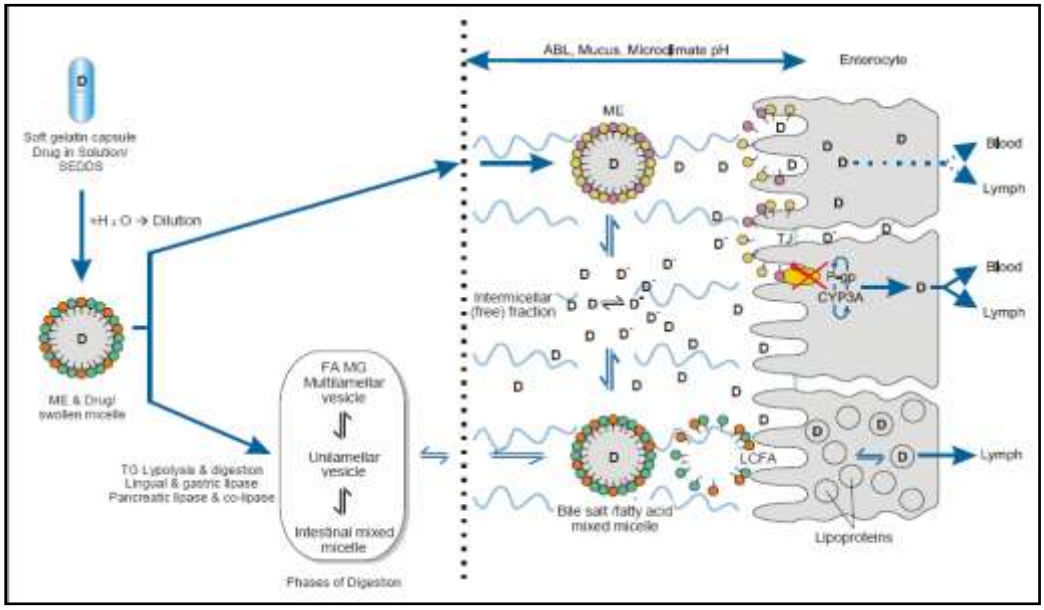

Figure 3. A graphical representation of *in vivo* fate of microemulsion.

CONCLUSION:

SNEDDS is a promising approach for BCS class II or IV drug compounds with poor aqueous solubility. Also chances of channelizing the API's through the lymphatic channels are possible, thereby limiting the hepatic first pass metabolism. 'Food Effect" of poorly water soluble drugs can also be minimized. This is the method suited for lipophilic drugs where resulting emulsification gives faster dissolution rates and absorption. The oral delivery of hydrophobic drugs can be made possible by SNEDDS which have been shown to substantially improve oral bioavailability. With future development of this technology SNEDDS will continue to enable

novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs, mainly BCS class-II and class-IV drugs.

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