CODEN (USA): IAJPBB ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

http://doi.org/10.5281/zenodo.495629

Available online at: http://www.iajps.com *Review Article*

SOLID SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS) DEVOLOPMENT, APPLICATIONS AND FUTURE PERSPECTIVE: A REVIEW

Febi S Kuruvila[1*], Flowerlet Mathew [2],S Kuppuswamy[3]
Department of Pharmacy, Nirmala College of Pharmacy, Muvattupuzha, Kerala.

Received: 21 March 2017 **Accepted:** 26 March 2017 **Published:** 28 March 2017

Abstract:
Developments in recent drug discovery programs, yields a large proportion of novel pharmacologically active molecules that are lipophilic and poorly soluble ,which is a major challenge for pharmaceutical researchers to enhance the oral bioavailability of such drug molecules. Compared to conventional oral dosage forms, Self nanoemulsifying drug delivery systems (SNEDDS) possesses potential advantages like ease of manufacture and scale up, quick onset of action, reduction in drug dose, reduction in inter and intra subject variability and food effects and minimize problems associated with filling of liquid SNEDDS in capsules. Several recent works on Self nanoemulsifying drug delivery systems suggests the commercial suitability of the system in improving the solubility and bioavailability of such drugs. The physicochemical properties, drug solubilization capacity and physiological fate considerably helps in the selection of the SNEDD components. The composition of the SNEDDS can be optimized mainly with the help of phase diagrams, whereas statistical experimental design can be used for further optimization. The transition of liquid SNEDDS to solid SNEDDS has also been accomplished by researchers. Solid-self nanoemulsifying drug delivery system focus on the incorporation of liquid/semisolid self nano emulsifying ingredient into solids by different solidification techniques like adsorption to solid carrier, spray drying, melt extrusion, nanoparticle technology and melt granulation. The present article gives more specification on spontaneous/rapid forming nanoemulsions or self nanoemulsifying systems for oral drug delivery by adsorption technique and gives complete information about formulation, method of preparation, characterization and application in solid dosage form of self nanoemulsifying drug delivery system.

Keywords:*Solid-self nanoemulsifying drug delivery system , Pseudo ternary phase diagram, Bioavailabilit,solubility,permeability.*

Corresponding author:
Febi S Kuruvila
Department of Pharmaceutics,
M.Pharm Student,
Nirmala College of Pharmacy,
Muvattupuzha, Kerala, India.
E-Mail: *febi.jais@gmail.com*

QR code

Please cite this article in press as Febi S Kuruvila et al, ***Solid Self Nanoemulsifying Drug Delivery System (SNEDDS) Devolopment, Applications and Future Perspective: A Review****, Indo Am. J. Pharm. Sci, 2017; 4(03).*

INTRODUCTION:

Nanotechnology has become a most promising technology in pharmaceutical sciences and it astonishingly influenced drug delivery research over the last two decades and various efforts are ongoing to extend its applications in various streams of pharmaceutical sciences,for example many nanoscale carriers have been recently explored for improving therapeutic performance of drugs. Different ways through which nanoscale technologies improves the therapeutic efficacy of drugs are:

- Improves solubility of hydrophobic drugs (Class II and IV drugs as per the Biopharmaceutical Classification System [BCS]);
- Improves permeability or transport of poorly permeable drugs (class III and IV drugs as per the Biopharmaceutical Classification System [BCS]);
- Modulates distribution and drug disposition of drugs;
- Prevents degradation of drugs in physiological milieu;
- Enables targeted delivery of the drugs to the site of action.

Self nanoemulsifying drug delivery system is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/ lipophillic drugs and to improve the oral bioavailability of poorly absorbed drugs[1,2].

Biopharmaceutical classification system

The BCS is a scientific framework for classifying drug substances based on their aqueous solubility and intestinal permeability. When combined with the dissolution profile of the drugs, the BCS mainly takes into account three major factors that govern the rate and extent of drug absorption from solid oral dosage forms: dissolution, solubility, and intestinal permeability. According to BCS classification system, drug substances are classified as shown in **table 1.**

The FDA has set specifications regarding the solubility and permeability class boundaries used in BCS classification.

Solubility: A drug substance is considered highly soluble when the highest dose strength is soluble in less than or equal to 250 ml of aqueous media at a pH range of 1 to 7.5 (equilibrium solubility at 37°C).

Permeability: In the absence of evidence suggesting instability in the gastrointestinal tract, a drug substance is considered to be highly permeable when the rate or extent of absorption in humans is determined to be greater than or equal to 90% of an administered dose based on the mass balance determination or by comparison with an intravenous reference dose (absolute bioavailability study).

SNEDDS are mainly useful for improving the rate and extent of absorption of hydrophobic or lipophilic drugs that comes under Class II and IV of Biopharmaceutical Classification System (BCS) (with low solubility), which exhibits a dissolution rate limited absorption.

Table 1*:* Examples of BCS Class II & IV Drugs

CLASS II	CLASS IV
Artemeter	Albendazole
Bicalutamide	Acetazolamide
Carbamazepine	Azathioprine
Dapsone	Bifonazole
Efavirenz	Didancosine
Ezetimibe	Furosemide
Folic Acid	Hydrochlorothiazide
Glibenclamide	Indinavir
Griseofulvin	Mesylate
Haloperidol	Nelfinavir
Ibuprofen	
Phenytoin Sodium	

Self nanoemulsifying drug delivery systems (SNEDDS)

Self nanoemulsifying drug delivery systems (SNEDDS) are regarded as nanoemulsion preconcentrates or as anhydrous forms of the nanoemulsion. Self-nanoemulsifying drug delivery systems are homogenous liquid mixtures consisting of drug , natural or synthetic oil , surfactant and cosurfactant that have a unique ability of spontaneously forming fine oil-in-water (O/W) nano-emulsions of size approximately 200 nm or less, upon dilution with water and under conditions of gentle or mild agitation similar to those which would be encountered in gastrointestinal tract (GIT) by the digestive motility of the GIT inside the body. SNEDDS are thermodynamically stable and transparent or translucent system. Nonionized Dispersion of (O/W) nanoemulsion was stabilized by addition of surfactant and co-surfactants. The Self nanoemulsifying drug delivery system is also known as Nanoemulsion, Miniemulsion, ultrafine emulsion, Submicron emulsion. The self-nanoemulsifying drug delivery system was formulated mainly by using medium chain triglycerides oils and non-ionic surfactant, which is important in oral ingestion. The SNEDDS is one of the stable nanoemulsion and it provides a large interfacial area for partitioning of drug between oil and aqueous phase,thereby improves the rate of drug dissolution and increases bioavailability of drug formulation. SNEDDs are the most preferred drug delivery system due to their stability , practicability of easy oral administration

and ability to improve drug self emulsification inside the gut[3,4].

In Self Nanoemulsifying drug delivery systems:

- Oil droplet size is: <100nm
- Appearance of dispersion is optically clear
- Required HLB value is >12
- Devolopment may require characterisation of Pseudo ternary phase diagram.

Types of Nanoemulsion (SNEDDS)

i. **Water in oil (W/O) Nanoemulsion**
In which droplet of water was dispersed in Continuous Phase oil.

ii. **Oil in water (O/W) Nanoemulsion**
In which oil droplet was dispersed in Continuous Phase Water.

iii. **Bi-continuous Nanoemulsion**
In which surfactant was soluble in both oil as well as water phase, and droplet was dispersed in both oils as well as water phase.

Advantages of Self Nano Emulsifying Drug Delivery System (SNEDDS)

- Ease of manufacture and scale-up.
- Protection of sensitive drug substances from the hostile environment in gut by providing a large interfacial area for partitioning of the drug between oil and water .
- Selective targeting of drug(s) toward specific absorption window in GIT.
- Enhanced oral bioavailability by increasing solubility and reducing the dose , thereby promoting efficient drug transport.
- Quick onset of action.
- Self nanoemulsifying drug delivery system (SNEDDS) has a much larger surface area and free energy than micro emulsions (SMEDDS).
- Reduction in inter-subject and intra-subject variability and food effects.
- Ability to deliver peptides which are more prone to enzymatic hydrolysis inside the GIT.
- Does not influence lipid digestion process unlike other lipid based drug delivery systems.
- More consistent temporal profiles of drug absorption.
- Control of delivery profiles.
- When polymer is incorporated in composition of SNEDDS it gives prolonged release of medicament.
- Fine oil droplets would pass rapidly and promotes wide distribution of the drug throughout the GIT, hence minimizing the irritations encountered during extended contact of bulk drug substance and the gut wall.
- The amenability of converting SNEDDS into solid self nanoemulsifying systems permits the development into a solid dosage form.
- It is used as Ayurvedic system and Unnani system.

Disadvantages of Self Nano Emulsifying Drug Delivery System (SNEDDS)

- Drugs which are administered at very high dose are not suitable for SNEDDS.
- The drugs exhibiting limited solubility in water and lipids are most difficult to administered as SNEDDS.
- The potential of SNEDDS in maintaining the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase.
- If the surfactant or co-surfactant contributes to a greater degree for drug solubilization, more would be the risk of precipitation .
- The stability of Self nanoemulsifying drug delivery system was affected by temperature and pH.

Mechanism of self- emulsification

The theory of formation of Self emulsification suggested by Reiss states that , emulsification occurs when the entropy change that favours the dispersion is greater than the energy required to increases the surface of dispersion, hence the free energy(ΔG) of conventional emulsion is (negative)direct function of energy required to create new surface between the two phases (oil and water phase) and the emulsion was stabilized .

The free energy of conventional emulsion is associated with ΔG, and can be described by the equation,

- $\mathbf{\Delta G = \Sigma N \pi r^2 \sigma}$

Where,

ΔG = free energy associated with the process
N = number of droplets
r = Radius of droplets
б = interfacial energy

The two phases of emulsion, tends to separate with respect to time to reduce the interfacial area, and eventually, the emulsion is stabilized by emulsifying agents.

Approaches for preparation of nanoemulsion

- **Low energy approach** also called the condensation method, require low energy for the fabrication of nanoemulsions and is based on the phase transitions taking place during the emulsification process.This method mainly dependent on modulation of interfacial phenomenon or phase transitions and intrinsic physicochemical properties of the surfactants, co-surfactants and oil to yield nano-

sized emulsion droplets.The low energy method is interesting as it utilizes the stored energy of the system to form smaller droplets. This emulsification can be brought about by the changes in parameters which may affect the hydrophilic lipophilic balance (HLB) of the system like temperature, composition, etc. The most commonly used low-energy emulsification methods include:

1. ***Phase Inversion Temperature (PIT) method*** ,which is an important method for preparation of nanoemulsion and microemulsion. The method is mainly based on the response to temperature. In this type of method many physical changes occuring that includes physicochemical changes, particle size and *in vivo - in vitro* drug release rate. This method also make use of the change in spontaneous emulsion formation. The non-ionic surfactant can be achieved by changing the temperature of the system. The forces in transition forms, O/W nanoemulsion at low temperature and W/O nanoemulsion at higher temperature.
2. ***Solvent displacement method*** for spontaneous fabrication of nanoemulsion has been adopted from the nano precipitation method used in polymeric nanoparticles. In this method, oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol and ethyl methyl ketone. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous or rapidly forming nanoemulsion by the occurance of rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation.
3. ***Phase Inversion Composition Method (Self-nanoemulsification Method)*** generates nanoemulsions at room temperature without the use of any organic solvents and heat. Forgirani *et al.* in their study observed that kinetically stable nanoemulsions with smaller droplet size (~50 nm) can be generated by the stepwise addition of water into solution of surfactant in oil, with gentle stirring and at constant temperature[6]. Although the components used in the above investigation were not of pharmaceutical grade, and it has opened doors to design pharmaceutically acceptable nanoemulsions using the similar approach.

- **High energy approach** for the formation of nanoemulsion high energy is applied and is mainly based on the selected composition of mixture,and also on the mixture containing surfactant, cosurfactant, cosolvents and other functional compound . The emulsification undergoes mechanical processing to from nanoemulsion.

  1.High Pressure Homogenizer is one of the important device for detection and preparation of fine emulsion, mainly to produce nanoemulsions. This method is important in which the oil /water surfactant mixture under very high pressure and the mixture was pumped by resistive valve. The very high shear stress is responsible for the formation of very fine emulsion droplets. The combination of the two theories, turbulence and cavitation, explains about the droplet size reduction during homogenization process. The high velocity of resultant mixture gives the liquid high energy in the homogenizer valve and generates intense turbulent eddies of the same size as a mean diameter droplet (MDD). Droplets were apart from Eddie currents resulting in a reduction in droplet size. Simultaneously, the pressure drop across the valve, cavitation occurs and generates further eddies disruption droplets. Decreasing the gap size ultimately increases the pressure of the droplet,and is responsible for greater degree of cavitation. Emulsion droplet having diameters < 100 nm can be produced using this method if the sufficient amount of surfactant present to completely cover the mixture of oil-water interface formed and the adsorption kinetics was high, is important to prevent droplet coalescence.

  2.Microfluidizatiion is an important method to detect and prepare nanoemulsion. The Micro fluidization is achieved by a device called 'Micro Fluidizer". This type of device is used in high pressure positive displacement pump (500-300 PSI) which forces the product through the interaction chamber, which consists of small channel droplets called micro channels. The product flows through the micro channels onto the impingements area which results in very fine particles of submicron range i.e. Nanoemulsion. The two solutions containing mixture of aqueous phase and oil phase system are under combination and are formed in the inline homogenizer to yield a coarse emulsion. The coarse emulsion under processing of a micro fluidizer and it undergoes further processing to from homogeneous, transparent and stable nanoemulsion.

  3.Sonication Method is important for determination of size of droplet and it is important for reduction of droplet size of conventional emulsion with the help of sonication mechanism. It is only applicable for small batches of nanoemulsion.

FORMULATION COMPONENTS AND CONSIDERATIONS OF SNEDDS

For the successful formulation of SNEDDS, requires thorough understanding of the spontaneous nanoemulsification process and also on the physicochemical as well as biological properties of the components used in the fabrication or

development of SNEDDS. The factors influencing the phenomenon of self nanoemulsification are:

- The physicochemical nature and concentration of oily phase, surfactant and cosurfactant or solubilizer (if included) ;
- The ratio of the components, especially oil to Smix ratio (surfactant :cosurfactant) ;
- The temperature and pH of the aqueous phase where nanoemulsification would occur;
- Physicochemical properties of the drug, such as hydrophilicity and lipophilicity, pKa as well as polarity.

The above stated factors should be given attention while formulating SNEDDS. In addition, the acceptability of the SNEDDS components for the desired route of administration is an important factor in the formulation of SNEDDS.

Formulation considerations with respect to the components of SNEDDS are discussed below:

Drug (Active pharmaceutical ingredient):

The self nanoemulsifying drug delivery (SNEDDS) system is a novel approach for enhancing oral bioavailability of the poorly water soluble drugs. Drug candidate should be soluble in oil phase as this influence the ability of SNEDDS to maintain the API in solubilised form. High melting point drugs with log P values of about 2 are poorly suitable for SNEDDS. While, lipophilic drugs having log P values greater than 5, are good candidate for SNEDDS. It is important to know that the therapeutic agent of interest can also have significant impact on the various aspects related to SNEDDS, such as phase behavior and nanoemulsion droplet size. Various physicochemical properties of the drug, such as log P value , pKa, molecular structure and weight, presence of ionizable groups and the quantity also have considerable effects on the performance of SNEDDS. Examples: Nifedipine, Albendazole,Cyclosporine, Atorvastatin calcium, Fenofibrate, Loratadine, Atenolol, Ibuprofen ,Ubiquinone, and Ezetimibe etc.

- **Other Components**

Self Nanoemulsifying drug delivery system also consists of

a) ***Oil Phase :*** In self nanoemulsifying drug delivery system (SNEDDS) , selection of specific oily phase is very important parameter as it is mainly associated with o/w nanoemulsion. Usually, the oil having maximum solubilizing potential for the selected drug candidate is mainly selected as an oil phase in the formulation of SNEDDS. This helps to achieve the maximal drug loading in the SNEDDS. At the same time, the selected oil should also be able to yield a nanoemulsions with smaller droplet size. Hence, the choice of the oily phase is often a compromise between its ability to solubilize the drug and its ability to form a nanoemulsion with desired characteristics. The oil which solubilises the lipophilic drug in a specified amount and that facilitates self emulsification and also increases the fraction of the lipophilic drug molecule transported via the intestinal lymphatic system. The lipophilicity of the oil and the concentration of oily phase in SNEDDS are directly proportional to the nanoemulsion size. The concentration of oil present in SNEDDS is about the 30-75% , modified and hydrolyzed vegetable oils are widely used because they show more solubility and self emulsification property. Oils with long chain and medium chain triglycerides(having surfactant property) are commonly used. Solvent capacity for less hydrophobic drugs can be improved by blending of triglycerides with mono- and di-glycerides. Triglycerides are highly lipophilic and the solvent capacity of drugs is a common function of the effective concentration in ester groups, and they are classified as short chain triglycerides (5 carbons or less), medium chain triglycerides (6-12 carbons atoms), or long chain triglyceride (12 carbons or greater) helps to decrease the degree of unsaturation and is important in preventing oxidative degradation. It is also a known fact that oils with relatively long hydrocarbon chains, such as fixed oils (e.g., soybean oil) or long chain triglycerides, are more difficult for nanoemulsification, whereas oils with moderate chain length (MCTs) and oils with relatively short chains (or low molecular volume), such as medium chain monoglycerides and fatty acid esters (e.g., ethyl oleate), having higher solvent capacity and ability for resistance to oxidation as compared to long chain triglycerides molecules are easy to nanoemulsify. The naturally as well as synthetically occurring mixtures of oils and fats are triglycerides containing long chain fatty acids(LCTs). The choice of oily phase depends on the ability of the solubilized drugs and it's ability to form nanoemulsion with desired characteristics. The oil used also increases friction to transport drug into the intracellular compartment to increases water solubility of less water soluble drug. For example, the mixtures of fixed oil and MCTs is important for maintanence of appropriate balance between loading capacity of drug and nanoemulsification. Thus, the long chain and medium chain triglycerides under different degrees of saturation is important to be used for designing of SNEDDS. Now days, the MCT have been replaced by novel semi synthetic MCTs to influence the water solubility of poorly soluble

drugs and oil phases are modified by vegetable oils, digestible or non-digestible oils and fats such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil and their hydrogenated oils for better solubility. Interestingly, long chain triglycerides have demonstrated great ability for improving intestinal lymphatic transport of drugs that are responsible in preventing first pass metabolism of drugs, compared with medium chain tri, di and mono-glycerides, whereas medium chain mono and diglycerides have greater solubilization potential for hydrophobic drugs as well as permeation enhancing properties[7,8]. It may be a difficulty for a single oily component alone to have optimum properties with respect to nanoemulsification and drug delivery. In such cases, a mixture of oils can be employed to meet optimum properties of the oil phase. A similar concept has been utilized in both nanoemulsions and microemulsions.

Table 2: Commonly used oily phases.

CLASS	EXAMPLE	COMMERCIAL NAME	APPLICATION
Fixed Oils	Soybean oil, castor oil, Sunflower oil, Olive oil , Cotton seed oil		P/O/T/Oc/M
Medium Chain Triglycerides(MCTs)	Triglycerides of capric/caprylic acids	Miglyol 810 & 812, Labrafac CC, Labrafac PG,Crodamol GTCC, Captex 300, 355	P/O/T/Oc/M
	Triacetin	Captex 500,300 & 355	P/O/T/Oc/M
Medium Chain mono and di-glycerides	Monoand diglycerides of capric/caprylic acids	Capmul MCM, Imwitor 742, Akoline MCM	O/T
Longchain Monoglycerides	Glyceryl monooleate	Peceol, CapmulGMO	O/T
	Glyceryl monolinoleate	Maisine35	O/T
Propylene glycol fatty acid esters	PG monocaprylate	Capryol 90, Capmul PG8, Sefsol 218	O/T
	PG monolaurate/dilaurate	Lauroglycol 90, Capmul PG12, Lauroglycol FCC	O/T
	PG dicaprylate/caprate	Miglyol 840, Captex 200	O/T
Fatty acid esters	Ethyl oleate	Crodamol EO	P/O/T/Oc/M
	Isopropyl myristate		P/T/Oc/M
	Isopropyl palmitate		P/T/Oc/M
Fatty acid	Oleic acid	Crossential O94	O/T/M
	Caprylic acid		O/T/M
Vitamins	Vitamin E		P/O/T/Oc/M

P: Parenteral ; O: Oral; T: Topical (dermal); Oc: Ocular; M: Mucosal.

b)Surfactant

Surfactant are defined as molecules and ions that are adsorbed onto the interface which prevent the interfacial tension and provide interfacial area. It is major component for preparation of nanoemulsion and helps to solubilise poorly water soluble drug. The choice of surfactant is also critical for the formulation of SNEDDS. A variety of surfactants are available for formulation of SNEDDS, which can be used either alone or as combination to obtain nanoemulsions with desirable characteristics at the same time that avoids or minimizes unfavorable effects offered by the surfactants.The molecule of surfactant is obtained in natural as well as synthetic origin. The properties of the surfactant which have greater influence on the nanoemulsification process, self nanoemulsification region and the droplet size of nanoemulsion are HLB (in oil), cloud point, viscosity and affinity for the oily phase.

Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of O/W droplets and rapid spreading of the formulation in the aqueous media. Surfactants are mainly amphiphilic in nature and they can dissolve or solubilise relatively high amounts of hydrophobic drug compounds and can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules. The most widely non-ionic surfactant with a relatively high hydrophilic-lipophilic balance (HLB >12) at 30-60% w/w concentration are used for formulation of stable SNEDDS. Use of double chain Surfactants eg; Aerosol OT, DDAB in the system prevents the use of Cosurfactants.

The concentration of the surfactants used in formulating SNEDDS considerably influence the droplet size of nanoemulsions, so it should be clearly noted that the surfactants used are not innocuous and they have favorable or unfavorable biological effects depending upon the chemical nature and concentration of the surfactant.The acceptability of the selected surfactant for the desired route of administration and its regulatory status (e.g., generally regarded as safe) must also be considered during surfactant selection. Optimum amount of surfactant unit is used for preparation of nanoemulsion but large quantity of surfactant can cause chemical toxicity . Certain surfactants might cause irritation to the GI mucosa and skin at higher concentrations. Thus, limited number of surfactants are orally acceptable. It is also noteworthy that the unfavorable characteristics associated with the surfactant may get diminished after association of it with the oily phase.For example, the hemolytic ability of surfactants was greatly reduced after their association with oily phase in submicronic emulsions.The most commonly used surfactants are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate. Hence the safety is major considerable parameter for selection of surfactant molecule. The lipid mixtures of molecules with higher surfactant - cosurfactant and oil ratios lead to the formation of SNEDDS and is responsible for enhancement of oral bioavailability of poorly water soluble drugs. Thus, the selection of surfactant is crucial for the formulation of SNEDDS and the surfactant concentration in SNEDDS should be kept at a minimal level as possible.

Classification surfactant molecule

Surfactant molecule is mainly classified as;

- ***Anionic surfactants***
- ***Cationic surfactants***
- ***Ampholytic surfactants***
- ***Non-ionic surfactants***

Anionic Surfactants

The hydrophilic group carries a negative charge is known as anionic surfactant. The negatively charged group such as carboxyl (RCOO-), sulphonates (RSO3 -) or sulphate (ROSO3-).

Examples : Potassium laurate, sodium lauryl sulphate.

Cationic surfactants

The hydrophilic group which have a positive charge is known as cationic surfactant.

Example : Quaternary ammonium halide.

Ampholytic surfactants / Zwitter or Zwitterionic surfactants

The surfactant units consisting of both charges i.e., positive and negative charge.

Example : sulfobetaines.

Non-ionic surfactants

The hydrophilic group with no charge but derives its water solubility as it can hold a strong polar functional groups like hydroxyl or polyoxyethylene (OCH2CH2O).

Examples : Sorbitan esters (Spans 20), Polysorbates (Tween 20).

Table 3: Commonly used surfactants.

CLASS	EXAMPLE	COMMERCIAL NAME	APPLICATION
Polysorbates	POE 20 sorbitan monooleate Tween® 80,	Crillet 4	P/O/T/Oc/M
	POE20sorbitan monolaurate Tween 20,	Crillet 1	P/O/T/Oc/M
Sorbitan esters	Sorbitan monooleate Span® 80,	Crill 4	P/O/T/Oc/M
	Sorbitan monolaurate Span 20,	Crill 1	P/O/T/Oc/M
	Sorbitan monostearate Span 60,	Crill 3	O/T/M
PEO–PPO–block copolymers	Poloxamer 188	Pluronic®/Lutrol F 68	P/O/T/Oc/M
	Poloxamer 407	Pluronic/Lutrol F 127	O/T/Oc/M
POE castor oil	POE35 castor oil	Cremphor® EL, Etocas 35 HV	P/O/T/Oc/M
POE hydrogenated castor oil	POE40 hydrogenated castor oil	Cremophor RH 40, HCO40, Croduret™ 40 LD	P/O/T/Oc/M
	POE60 hydrogenated castor oil	Cremophor RH 60, HCO60	P/O/T/Oc/M
POEstearate	PEG66012 hydroxystearate	Solutol HS 15®	P/O/T/Oc/M
POE vitamin E	Tocopheryl PEG 1000 succinate	Vitamin E TPGS	O/T/Oc/M
Sucrose esters	Sucrose laurate		P/O/T/Oc/M
	Sucrose palmitate		O/T
Polyglycolyzed glycerides	Linoleoyl macrogol glycerides	Labrafil® 2125 CS	O/T
	Oleoyl macrogol glycerides	Labrafil 1944 CS	O/T
	Caprylocaproyl macrogol glyceride	Labrasol®	O/T
	Polyglyceryl oleate	Plurol® oleique CC 497	O/T
	Lauroyl macrogol glycerides	Gelucire® 44/14	O/T
	Stearoyl macrogol glycerides	Gelucire 50/13	O/T
Phospholipids	Soybean lecithin		All Routes

P: Parenteral ; O: Oral; T: Topical (dermal); Oc: Ocular; M: Mucosal; PEG: Polyethylene glycol; POE: Polyoxyethylene;TPGS: Tocopheryl polyethylene glycol 1000 succinate.

c) Co-surfactant

The most important role of co-surfactant in SNEDDS is reduction of oil-water interface and provide the larger surface area and allow the spontaneous formation of nanoemulsion. The coemulsifier or cosurfactant and/or solubilizer present in SNEDDS facilitates nanoemulsification and improves the drug incorporation. In addition they modulates Self nanoemulsification time and droplet size of nanoemulsion. In SNEDDS, generally co-surfactant of HLB value 10-14 is used. It is important to increasing oral bioavailability of poorly water soluble drugs. Co-surfactant was added at a concentration of 0-30% w/w along with surfactant unit or in combination of surfactant units to increase the ability of surfactants in improving water solubility of the poorly soluble drug. Lipophillic cosurfactant posses better miscibility with MCT and better ability to promote emulsification. Most single-chain surfactants do not lower the oil-water interfacial tension sufficiently to form nanoemulsion nor are they of the correct molecular structure because the single chain co-surfactant may prevent the interfacial fluidity. The co-surfactant molecule when comes in contact with surfactant, oil and water it gets separated by monomolecular layer of surfactant molecule.The Monomolecular Layer of Surfactant molecule is known as Liquid Crystal formation layer. The most important application of cosurfactant in self nanoemulsifying drug delivery system is to prevent interfacial tension between oil and water interface.

Table 4: List of commonly used solubilizers.

CLASS	EXAMPLE	APPLICATION
Shortchain alcohols	Ethanol, benzyl alcohol , Akoline MCM®	P/O/T/Oc/M
Alkane diols and triols	Propylene glycol, Lauroglycol™ FCC	P/O/T/Oc/M
	Glycerol	P/O/T/Oc/M
Polyethylene glycols	PEG 400, Poloxamer 188	P/O/T/Oc/M
Glycol ethers	Diethylene glycol monoethyl ether (Transcutol®)	O/T

P: Parenteral ; O: Oral; T: Topical (dermal); Oc: Ocular; M: Mucosal.

Cosurfactants can be incorporated into SNEDDS for different purposes, such as:

- For increasing the drug loading in SNEDDS; For modulating the self nanoemulsification time of nanoemulsion;
- For reducing droplet size of nanoemulsion.

Therefore, surfactants (i.e.,hydrophilic or lipophilic) and/or amphiphilic solubilizers with pharmaceutical acceptability and suitability are used for this purpose. The incorporation of the coemulsifiers or solubilizers in SNEDDS may also helps in expansion of nanoemulsification region in the phase diagrams.

Aqueous Phase

The nature of aqueous phase where SNEDDS are introduced would greatly influence the droplet size and stability of nanoemulsion. Such factors affecting nanoemulsion characteristics include:

a. pH and ionic content of aqueous phase,
b. Electrolytes or various ions in the physiological milieu .

Since the physiological milieu has diverse pH ranges varying from pH 1.2 (pH in stomach) to 7.4 and greater (pH of blood and intestine) and the pH of aqueous phase can have a dramatic influence on the phase behavior of the SNEDDS, especially when a drug with pH dependent solubility is loaded in the system.

Hence, it is desirable to evaluate the self nanoemulsification time as well as the characteristics of the resultant nanoemulsion in aqueous phases with varying pH and/or electrolyte concentration (depending on the type of application). Therefore, in addition to plain water, Ringer's solution, simulated gastric fluid (pH 1.2), simulated intestinal fluid (pH 6.8) and phosphate buffered saline are used as aqueous phase to evaluate the spontaneous nanoemulsification of SNEDDS.

METHODS OF PREPARATION OF LIQUID SNEDD:

Self Nanoemulsifying drug delivery system (SNEDDS) are prepared by two ways:

1. *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 the filtrate was taken and are diluted with ethanol or suitable solvents and assayed accordingly for the determination the free drug concentration in the vehicle.

2. *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.

Steps for formulation of SNEDDS in brief

- Selection of oil, surfactant and co-surfactant on the basis of drug compatibility and solubility study.
- Construction of pseudo-ternary phase diagrams.
- Selecting ratio of surfactant/co-surfactant and oil on the basis of pseudoternary phase diagrams.
- Optimization of SNEDDS formula.
- Evaluation of Liquid SNEDDS.
- Selection of best formulation from different formulation of SNEDDS based on data obtained after evaluation studies.
- Conversion of the optimized formulation to solid by adsorbing it on an absorbent carrier.
- Evaluation of solid SNEDDS.

Selection of components for SNEDD preparation:

- ***Oil (solubility studies):*** The solubility of drug in various buffers, oils, surfactants, and co-surfactants was measured by shake flask method as suggested by Date and Nagarsenker. An excess amount of drug was placed into an eppendorf tube containing 2 ml oil followed by sealing in vials. The resultant mixture were heated on a water bath at a temperature of 40°C and are stirred vigorously using vortex mixer (Cyclomixer) for 5 min for facilitating the

solubilization. Sealed vials were then stirred in a water bath at a temperature of 40°C for 24 h and are kept at 30°C for 72 h for reaching the equilibrium. Each vial was then centrifuged at 15,000 rpm for 10 min using a centrifuge followed by the removal of undissolved drug by filtering with a membrane filter (0.45 µm). Samples were suitably diluted with appropriate solvents and a drug concentration was obtained via a validated UV method at specific absorbance using a double-beam UV visible spectrophotometer. The experiment was repeated thrice for better results and were represented as mean values (in mg/mL ± SD).

- ***Surfactant (Emulsification Study):*** Surfactants were selected based on percent transparency and ease of emulsification with the selected oil phase. Specified amount(300 mg) of each surfactant were added to specified amount(300 mg) of selected oil in different test tubes at a ratio of 1:1. The mixtures were then heated gently for facilitating homogenization. Then, 50 mg from each of the mixture was diluted with 50 ml distilled water in a corked conical flask. To know the ease of emulsification , the number of flask inversions required to obtain a homogeneous emulsion were noted. Emulsions were then allowed to stand for a period of atleast 2 h and the optical clarity of the aqueous dispersion was assessed visually in a qualitative manner and UV-VIS spectrophotometer were used for measuring the amount of light of given wavelength transmitted by the solution. The emulsions were further observed for any turbidity or phase separation.

- ***Co-surfactant (emulsification study) :*** Co-surfactants were screened for SNEDDS formulation . The screening of the cosurfactant was conducted on the basis of percentage transparency as well as ease of emulsification. Mixtures of 100 mg of the co-surfactant, 200 mg of the selected surfactant, and 300 mg of the selected oil were prepared and evaluated in a similar fashion as in the above section on surfactants and were evaluated similarl .

Drug-Excipient Compatibility study by Fourier Transform Infrared Spectroscopy:

The infrared absorption spectra of drug and mixture of drug with excipients in ratio 1:1 were obtained in a potassium bromide disk to determine any interaction between the drug and excipients. The spectra were recorded on an IR-1600 Perkin Elmer infrared spectrophotometer.

Construction of Pseudoternary Phase Diagram

Pseudoternary phase diagram is important for determination of self nanoemulsifying drug delivery system (SNEDDS). It is diagrammatic representation of oil, surfactant and co-surfactant (Smix), water is known as Pseudoternary phase diagram. Pseudoternary phase diagram was constructed by Phase titration method and Phase inversion method. The preparation consists of solutions containing oil and different surfactant to co-surfactant ratio by weight such as 1:1, 2:1, 3:1 etc. These solutions were then vortexed for 5 min and an isotropic mixture will be obtained. Observe their appearance as whether turbid or clear. Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution would indicate the formation of a nanoemulsion (SNEDDS). The values were used to prepare Pseudo ternary phase diagram. This diagram corner can represent 100% concentration of each phase content. The diagram is important to give information related to binary mixture of two components such as surfactant/cosurfactant, water/drug or oil/drug. The Pseudoternary phase diagram is represent mixture of surfactant, co-surfactant, oil, and water phase as shown in Figure No.2. After the study of nanoemulsion region in the phase diagrams were done, constructed by using appropriate softwares like CHEMEX school software,Triplot software,Pro Sim Ternary Diagram Software etc.

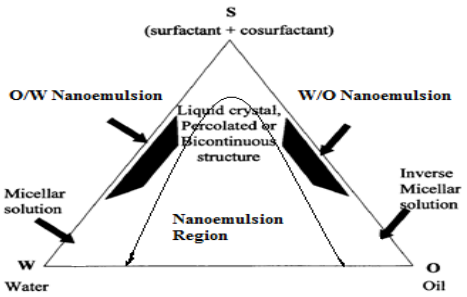

Fig 2: Pseudoternary phase diagram

Preparation of Liquid SNEDDS :

It is an important method for preparation of SNEDDS having the surfactant/co-surfactant(S_{mix}) ratio and oil/S/CoS ratio was selected from the psedoternary phase diagram. A number of series of the formulation was prepared by different concentrations of oil, surfactant and cosurfactant. The oil and surfactant was weighed in suitable proportions and drug was dissolved to this mixture and the dissolved mixture was stored at room temperature in sealed transparent bottles until used.

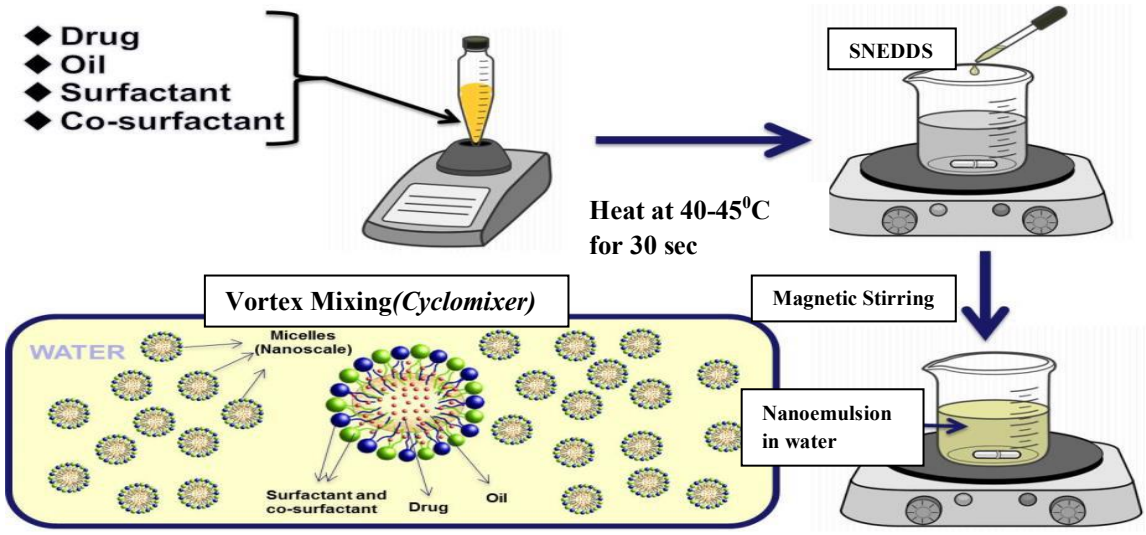

Fig 3: Formulation of Liquid SNEDDS

COMPONENT SCREENING, OPTIMIZATION & CHARACTERIZATION OF LIQUID SNEDDS

As talked about in the first place, the components of SNEDDS and their concentrations have profound effects on the various characteristics of nanoemulsions, such as droplet size, polydispersity index, self nanoemulsification time and in vitro drug release rate. Hence, it is important to optimize the amounts of the SNEDDS components after initial selection. The initial selection of the components can be on the footing of their ability to solubilize the drug of interest and also along their ability to form spontaneous nanoemulsions. After selecting potential components of SNEDDS, the phase behavior of the elements should be examined to identify various phases and phase modulations. After analyzing the phase behavior and identifying probable concentrations of the factors that might yield spontaneous nanoemulsions,which is important to plot a ternary diagram with surfactant, oil and coemulsifier or solubilizer to identify the self nanoemulsification region. The self nanoemulsification region in the ternary diagram is identified by evaluating the droplet size of the nanoemulsions resulting after diluting various compositions in the ternary diagram with the specified measure of water. All the details in the selfnanoemulsification region yield spontaneous nanoemulsion with droplet sizes of about 200 nm or lesser. Hence the purpose of the self nanoemulsfication region (in summation to the phase behavior study) helps in the optimizing SNEDDS and also for finalizing the SNEDDS composition for in vitro and in vivo studies. The optimization of SNEDDS can also be achieved with the help of optimization techniques like statistical experimental design or by response surface methodology. The

major advantage of the response surface methodology is that they can yield optimal SNEDDS (composition) with a minimum bit of experiments without compromising the final product characteristics. In response surface methodology, the influence of various variables on the characteristics of SNEDDS (e.g., Droplet size, self nanoemulsification time and in vitro dissolution) can be analyzed with a circumscribed number of experimentations. The statistical analysis is utilized to distinguish the impact of each variable along the features of the SNEDDS. In one case, when the mathematical correlation is shown between the variables and the response, response surface methodology can be applied to produce a product with desired features. Hence, SNEDDS composition with much reduced self nanoemulsification time, small droplet size and higher dissolution rate can be obtained by statistical experimental design techniques. Several optimization techniques such as Box Behnken design and D optimal design have been utilized by the investigators to optimize various characteristics of SNEDDS.

EVALUATION OF LIQUID SNEDDS

It is important to qualify the final SNEDDS for various parameters.

a) **Thermodynamic stability of emulsion:** The Thermodynamic stability of lipid based formulation is also crucial to its functioning, which can be adversely affected by precipitation of the drug in the excipients matrix. In addition to poor formulation thermodynamic stability can lead to phase separation of the excipients affecting not

only formulation performance as well as visual functioning.

b) **Centrifugation study:** The formulations were centrifuged using laboratory centrifuge at 5000 RPM for 30 minute**.** The resultant formulations were then determined for any instability problem, such as phase separation, creaming or cracking. A formulation which is stable is selected for further works.

c) **Heating and cooling cycle:** Three heating/cooling cycles between 4°C and 40°C with storage at each temperature for not less than 24 h. The resultant formulations were evaluated for their thermodynamic instability like phase separation and precipitation. A formulation which gives this test subjected for further examination.

d) **Freeze thaw cycle:** Freeze thawing was employed to assess the stability of SNEDDS. The formulations were subjected to 3 freeze-thaw cycles, which included freezing at −4°C for 24 h followed by thawing at 40°C for 24 h. Centrifugation was performed at 3000 RPM for 5 minute. The preparations were then observed for phase separation.

e) **Droplet Size:** Droplet size of (SNEDDS) was determined by photon correlation spectroscopy that analyses the fluctuations in light scattering due to Brownian motion of the particle, using a Zetasizer. The zeta potential of the SNEDDS should be evaluated as it may further give an idea of the colloidal stability. Light scattering was monitored at 25 ºC at a 90º angle. The optimized nanoemulsion sample was diluted with distilled water, placed in quartz corvette and subjected to droplet size analysis.

f) **Viscosity:** The Viscosity (rheological property) of the self nanoemulsifying drug delivery system (SNEDDS) was measured by Brookfield Viscometer for determination of consistency of nanoemulsion formulation**.**

g) **Stability study:** The Stability study is important to determine the quality as well as purity of nanoemulsion system. Stability helps in determining the tolerance of formulation. The different nanoemulsion formulations by subjecting them at mechanical stress conditions (centrifugation at 2000- 4000 RPM) as well as formulation was stored at different temperatures ranging from 4 ± 1 °C to 40 ± 1°C for different time intervals to define its stability. The outcome of the mechanical stress conditions on the photochemical stability of the nanoemulsion was observed by determining the percent phase separation, giving way of nomination or any physical modification. The fields having no relevant alteration in the formulations after 60 min of centrifugation at 2000 RPM were considered as stable. The chemical stability of the drug in SNEDDS should be assessed by carrying out long term storage stability studies as per the guidelines proposed by the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use.

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

i) **Dispersibility test:** The SNEDDS should be characterized for *in vitro* dissolution profile in various dissolution media. The efficiency of self-emulsification of oral nanoemulsion is determined by using a standard USP XXII dissolution apparatus II. One ml of each formulation is added to 500 ml of water at 37±0.5ºC. The stainless steel dissolution paddle rotating at 50 RPM provided gentle agitation. The in vitro performance of the formulations is visually found out by applying the following grading System.

Table 5: Visual Grading System

GRADE	TIME FOR EMULSIFICATION	OBSERVATION	VISUAL APPEARANCE
Grade A	Within 30 seconds	Rapidly forming nanoemulsion which is clear and transparent, high spreadability .	Bluish tinge
Grade B	Within 1min	Rapid nanoemulsion formation which is slightly less transparent, less clear	Bluish white tinge
Grade C	Within 2min	Rapid nanoemulsion formation, which is turbid in nature formed .	Milky white tinge
Grade D	Within or Longer than 3 min	Nanoemulsion devoid of or slow to minimal emulsification , with non uniform distribution of oil droplets	Dull, grayish white tinge having slightly oily appearance
Grade E	Longer than 3 min	Formulation exhibiting either less,poor or minimal emulsification	Large oil globules

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation which falls under Grade C could be recommend for SNEDDS as well as for SEDDS formulations.

j) **Morphological study**:
Morphological study is an important step to present informationsrelated to the external appearance of the formulation like color, odour, consistency, density**.** The morphology of the nanoemulsion droplets can be visualized, evaluated and detected by transmission electron microscopy (TEM).

k) **pH Measurements:**
The pH of nanoemulsion formulations was measured using a pH meter or Potentiometer. Electrodes were completely dipped into the semisolid or liquid formulations and pH was noted.

l) **Percent Transmittance:**
The percent transmittance of the nanoemulsion formulation (SNEDDS) was measured using UV Visible double beam spectrophotometer or Single Beam Spectrophotometer using distilled water as blank at suitable wavelength.

m) **Preparation of Solid SNEDDS:**
Drug was added into accurately weighed amount of oil in a screw capped vials and melted in water bath if necessary. Then the surfactant and co-surfactant were added to the oily mixture using a positive displacement pipette and stirred with a vortex to obtain homogeneous solution. Solid Self nanoemulsifying drug delivery system (S-SNEDDS) was prepared by adding selected liquid SNEDDS dropwise onto suitable novel adsorbents like Neusillin and are mixed well with gass rod. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and are stored until used.

Limitations of Liquid SNEDDS

Self nanoemulsifying drug delivery systems, being liquid in nature, need to be given up through either soft/hard gelatin or hydroxypropylmethylcellulose capsules. Liquid SNEDDS when filled in capsules a few issues may takes place, such as the incompatibility of components with the capsule shell when kept for long term, precipitation of drugs during fabrication and storage at low temperature and critical method of production compared to others. In addition, SNEDDS may not be useful for hydrophobic drugs that can undergo pH catalyzed or solution state degradation such as hydrolytic degradation at accelerated conditions of storage. Hence, chemical stability of drugs in SNEDDS needs to be studied at accelerated conditions.

Solid SNEDDS

The researchers realized that it's better to obviate disadvantages associated with liquid SNEDDS handling, manufacturing and stability by converting them to solid state. Solid dosage forms are most stable and are more convenient for handling; therefore, attempts are made to convert the liquid systems into solid SNEDDS. Hence, the concept of solid SNEDDS was developed. Solid SNEDDS in the form of dry, solid powders would thereby helps in overcoming the limitations associated with liquid SNEDDS. Various techniques, such as spray drying, freeze drying and adsorption on carriers, can be employed to convert liquid SNEDDS into solid SNEDDS and thus can be compressed into tablets. The selection of the particular process for preparation of the solid SNEDDS depends on the content of oily excipient in the formulation, properties of the active pharmaceutical ingredients, such as solubility, heat stability and compatibility with other ingredients.

The most simplest technique for converting liquid SNEDDS to solid SNEDDS by adsorption onto the surface of carriers such as Neusilin etc, or by granulation using liquid SNEDDS as a binder. This technique is not complicated, cost effective, easily optimized and industrially scalable. It can also be used for heat and moisture sensitive molecules, thus providing an advantage over other techniques like spray drying and freeze drying. Various excipients used in preparation of solid oral dosage forms can be employed for adsorption, provided they should possess large surface areas to adsorb sticky and viscous oily SNEDDS formulation.

Researchers has already proven the ability of different excipients like dibasic calcium phosphate, lactose, microcrystalline cellulose, colloidal silicon dioxide and Neusilin, to adsorb liquid SNEDDS. It was also found that conversion to solid form did not significantly alter the dissolution profile. Neusilin was found to improve free flowing property of powder with high bulk density.

Taha *et al.* adsorbed vitamin A loaded SNEDDS with microcrystalline cellulose as solid carrier and compressed the powder to obtain tablets[9]. The obtained Vitamin A loaded SNEDD tablet exhibited higher relative bioavailability of 143.68% when compared with tablets to which vitamin A oily solution was incorporated. The peak plasma concentration and area under the curve of vitamin A self nanoemulsifying tablet was also found to be higher in comparison with tablets of vitamin A oily solution.

Lutein SNEDDS were adsorbed on Aerosil 200 to obtain solid SNEDDS by Yoo *et al.*[10] . Dissolution of lutein from the solid SNEDDS was effected in less than 5 min in distilled water and showed no signs of precipitation or aggregation of the drug .

Mahmoud *et al.* have reported SNEDD tablet formulation of carvedilol, where granulated aerosil and microcrystalline cellulose were used as adsorbents and converted into a liquisolid tablets[11] and the tablets also retained the nanoparticle size of the nanoemulsion. The SNEDD tablet of carvedilol possess drug release properties similar to that of immediate release dosage form. The same group of scientists later have also identified the use of superporous hydrogel as a solid carrier for carvedilol SNEDDS[12] .

In some published literatures, very few reports have been found where solid self emulsifying systems are formulated using techniques such as spray drying, freeze drying and extrusion spheronization[13,14,15,16,17,18]. In Patil and Paradkar's work , they have employed polystyrene beads to deposit self emulsifying loratidine[22]. In a similar manner, such techniques can also be utilized for further development of solid self nanoemulsifying formulations .

Conversion to Solid Intermediates of Self Nanoemulsifying Formulation

Drug was added into accurately weighed amount of oil in a screw capped vials and melted in water bath if necessary. Then the surfactant and co-surfactant were added to the oily mixture using a positive displacement pipette and stirred with a vortex to obtain homogeneous solution. The optimized liquid SNEDDS was converted into free flowing powder ie.,Solid self nanoemulsifying drug delivery system (S-SNEDDS) was prepared by adding selected liquid SNEDDS dropwise onto suitable solid carriers (like Aerosil 200,Neusillin etc,) at 1:1 ratio by physical mixing in a small mortar and pestle. Resultant damp mass was passed through sieve no. 120 and dried at ambient temperature and are stored until used[19,20].

In brief, liquid formulation of SNEDDS was added drop wise over solid carrier contained in broad porcelain dish. After each addition, mixture was homogenized using glass rod to ensure uniform distribution of formulation. Adsorbed SNEDDS was passed through sieve No.44 and was dried at ambient temperature and filled in hard gelatin capsule of zero size, and are stored in suitable containers until further use.

Characterization of Solid SNEDDS

Based on the final dosage form of the solid SNEDDS i.e., tablet or a capsule, the powder properties of the solid emulsion particles are important. The nature and the quantity of liquid SNEDDS which is adsorbed onto the surface of a particular excipient would impact the properties of the obtained solid particles. The ratio of liquid : adsorbent quantity is important. Powder properties, such as density, angle of repose, flow property, compressibility index and particle size distribution, are important parameters for processing into dosage form. The globule size of the spontaneously formed nanoemulsion would also govern its performance *in vivo*. The desorption of SNEDDS from the surface of the solid particles and its conversion into nanoemulsion is the rate limiting step for the dissolution and absorption of the drug.It is necessary to carry out physical characterization of the solid SNEDDS using xray diffraction spectroscopy, differential scanning calorimetry (DSC)and scanning electron microscopy(SEM) to ensure that there is no drug precipitation during preparation of the solid SNEDDS. The absence of characteristic drug melting endotherm in differential scanning calorimetry suggests that the drug is in a solubilized state in solid SNEDDS. Xray diffraction is a useful technique employed in the characterization of crystalline materials. The formation of a diffuse diffraction pattern and the disappearance of characteristic drug peaks indicates that the drug is in a solubilized state in the solid SNEDDS. Scanning electron microscopy is useful technique to investigate the surface properties of the particles as well as their physical form. *In vitro* dissolution studies conducted gives an idea about the fate of the formulation in the GI tract.

Evaluation studies of the Powder Blend

a) Angle of repose

Angle of repose is the maximum angle that can be obtained between the surface of a pile of powder and the horizontal plane. The frictional force in a loose powder can be measured by the angle of repose. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle θ, is in equilibrium with the gravitational force. The angle of repose was determined by funnel method. The funnel was fixed at a particular height (2cm) on a burette stand. The powder sample was passed through the funnel until it formed a pile. Further adding of powder was stopped as soon as the pile touched the tip of the funnel. A circle was drawn across the base of the pile without disturbing the pile. Average radius was found by drawing 2-3 diameters in the circle. The same procedure was repeated for three times. The angle of repose was calculated using the equation,

$$\tan \theta = h / r$$

$$\theta = \tan^{-1} (h / r)$$

Where, θ = angle of repose

h = height of the powder cone in cm

r = radius of the powder

Table 6: Standard values of angle of repose

Standard values of Angle of Repose (θ in degrees)	Type of flow
< 20	Excellent
20 – 30	Good
30 – 40	Passable
> 40	Very poor

b) Bulk density (D_b)

The powder blend (10 g) was passed through sieve No.18 to break up agglomerates that may have formed during the storage and transferred into a dry 25 ml cylinder. Carefully levelled the powder without compacting and read the unsettled apparent volume, Vo, to the nearest graduated unit. Replicated the determination three times and calculated the bulk density in g per ml by the formula .

Bulk Density, $\mathbf{D_b = M / V_0}$

Where, M = mass of the powder sample

c) Tapped density (D_t)

The powder blend (10 g) was passed through Sieve No.18 to break up agglomerates that may have formed during the storage and transferred into a dry 25 ml glass graduated cylinder. The cylinder containing the sample was mechanically tapped by raising the cylinder and allowing it to drop under its own weight from a height of about 2 cm. The cylinder is tapped 500 times and measured the tapped volume Vf, to the nearest graduated unit. The experiments were done in triplicate and calculated the tapped density, in g per ml, by the formula.

Tapped Density, $\mathbf{D_t = M / V_f}$

Where , M = mass of the powder sample

V_f = Final tapped volume

d) Carr's compressibility index (I)

Carr's compressibility index (I), is an indication of the ease with which a material can be induced to flow. It is expressed in percentage. Carr's "percent compressibility" is calculated by the equation,

Compressibility Index, $\mathbf{I = (D_t - D_b) / D_t \times 100}$

Based on the I value, type of flow can be assessed. The values of I below 15% usually give rise to good flow characteristics, but those above 25% indicate poor flowability.

Table 7. Standard values for Carr's index

Carr's index (%)	Type of flow
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very , Very poor

e) Hausner ratio

Hausner ratio is an index of ease of powder flow; it is calculated using the formula,

$$\textbf{Hausner Ratio} = D_t / D_b$$

Powder classification as per Hausner ratio is given in the table 8.

Table 8. Standard values for Hausner ratio

Standard values for Hausner ratio	Type of flow
< 1.25	Good
> 1.25	Poor

f) *In vitro* release / dissolution study

The quantitative *in vitro* release test was performed using USP type II dissolution apparatus maintained at 37 ± 0.5°C.The dissolution medium used was 0.1N HCl (900 mL). The bsaket were rotated at 50 rpm. Samples required were taken and filled in "size 00"capsules. At specified time, 1 ml samples were withdrawn (5, 10, 15, 30, 45, 60 min) and replaced with fresh dissolution medium. Aliquots, after filtration through Whatman filter paper and analysis was carried out using UV spectrophotometer at 248nm.

Kinetics of in vitro drug release[23]

To study the release kinetics of in vitro drug release data was applied to kinetic models such as zero order, first order, higuchi and korsmeyer- Peppas.

Zero order

This model can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in the case of some transdermal systems, as well as matrix tablets with low soluble drugs, coated forms etc. The dosage forms following this profile release same amount of drug by unit of time and this model can be expressed as

$$\mathbf{Q_t = Q_0 + K_0 t}$$

Where, Qt Amount of drug dissolved in time't'

K_0 = zero order release constant

Q_0 = initial amount of drug in solution

First Order:

The pharmaceutical dosage forms following this dissolution profile, release the drug in a way that is proportional to the amount of drug remaining in its interior, in such way, that the amount of drug released by unit of time diminish. The following relation can be used to express this model.

$$\mathbf{\log Q_t = \log Q_0 + K_t .t / 2.303}$$

Where, Q_t: Amount of drug dissolved in time't'
Q_0: Initial amount of drug in the solution
K_t: First order release constant

Higuchi Model
This model helps to study the release mechanism of water-soluble and low water soluble drugs incorporated in semi-solid and solid matrixes. The mathematical expression for drug release is

$$Q = [D (2C-C_S) C_S.t] 1/2$$

Where, Q = Cumulative % of drug released in time't' per unit area.
C = Initial drug concentration
C_S =Drug solubility in the matrix media
D = Diffusion co efficient
Assuming that diffusion co efficient and other parameters remain constant during release, the above equation reduces to,

$$Q = k.t ½$$

Thus for diffusion controlled release mechanism, a plot of cumulative % of drug released Vs square root of time should be linear. The linearity of the plots can be checked by carrying out linear regression analysis and determination of regression coefficient of the plot.

Korsmeyer Peppas
To verify the fact that whether the diffusion follows fick's law or not, the drug release data can also be plotted according to peppas equation, in which log %cumulative release is plotted against log time according to peppas equation , the rate of drug release can be expressed as;

$$Q = Ktn$$

Taking log on both sides of the equation

$$Log Q = log K + n log t$$

Where Q is the % cumulative release of drug released, t is the time and n is the slope of linear plot of log Q v/s log t. The n value can be used to characterize the diffusional release mechanism and the data is given in the table 9. K is the diffusion rate constant and n is diffusional exponent

Table 9: Diffusion exponent and solute release mechanism.

Diffusion exponent (n)	Overall solute diffusion mechanism
<0.5	Quasi-Fickian diffusion
0.5	Fickian diffusion
0.5<n<1.0	Anomalous (non-Fickian) diffusion
1.0	Case-II transport
>1.0	Super case-II transport

Controlled release SNEDDS
The self-nanoemulsifying system can also be used in fabrication of extended release delivery systems for drugs that are poorly soluble. Patil *et al.* developed an extended release felodipine SNEDDS where Aerosil 200 was used as the gelling agent and the gelled SNEDDS were encased in a hydrophobic Gelucire 43/01[24] . Nazzal and Khan prepared Eutectic based solid SNEDDS of Coenzyme Q10 using the tableting technique with Kollidon® VA 64, Glucidex® IT 12, and Avicel® PH112 [26]. In this study , the researchers demonstrated that a tablet dosage form could be manufactured without any complicated manufacturing techniques to release a lipid formulation in a controlled release pattern. Common processing parameters, such as mixing time, compression force, amount of colloidal silicon dioxide and magnesium stearate, have a overwhelming effects on the release pattern of lipid containing formulations from their solid carriers.

SNEDDS: Potential Mechanism
The potential of SNEDDS in improving oral delivery of several therapeutic agents (belonging to various therapeutic classes) has been established by various *in vitro* and/or *in vivo* studies. The potential mechanisms responsible for improvement in oral bioavailability by SNEDDS are depicted in Figure 4. In most of the studies conducted so far have evaluated the pharmacokinetics of the drug when incorporated in SNEDDS and very few investigations demonstrated about their pharmacodynamic efficacy. Although pharmacokinetic studies are sufficient to establish proof of concepts for SNEDDS, the results of the pharmacokinetic study should preferably be collaborated by pharmacodynamic studies, for drugs such as Atorvastatin, Simvastatin, and Ezetimibe, which do not show any pharmacokinetic - pharmacodynamic correlation.

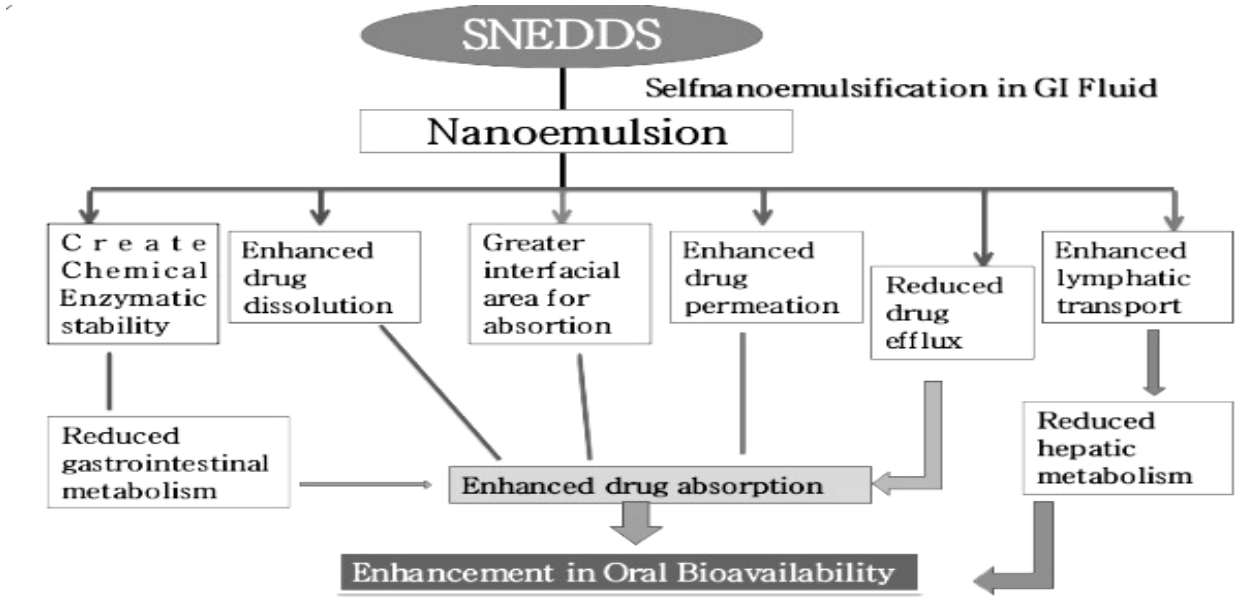

Fig 4:Potential Mechanism for improving bioavailability of SNEDD when taken orally

Marketed Formulations of SNEDD

Some examples of SNEDD formulation that are currently available in the market are listed in table below:

Table 10: Marketed Formulations of SNEDD

Drug Name	Trade Name	Manufacturer	Dosage Form	Indication
Amprenavir	Agenerase	Galaxosmithkline	SGC	HIV Antiviral
Bexarotene	Targretin	Novartis	SGC	Antineoplastic
Calcitriol	Rocaltrol	Roche	SGC	Calcium Regulator
Cyclosporine A/I	Neoral	Novartis	SGC	Immuno-suppressant
Cyclosporine A/I	Sandimmune	Novartis	SGC	Immuno-suppressant
Cyclosporine A/III	Gengraf	Abbott Laboratories	HGC	Immuno-suppressant
Fenofibrate	Lipirex	Sanofi-Aventis	HGC	Anti-hyperlipidemic
Ritonavir	Norvir	Abbott Laboratories	SGC	HIV Antiviral
Saquinavir	Fortovase	Hoffman-La Roche Inc	SGC	HIV Antiviral
Valproic Acid	Convulex	Pharmacia	SGC	Antiepileptic

Applications of nanoemulsion in drug delivery

Self nanoemulsion have been applied in various aspects of drug delivery including Cosmetics and transdermal drug delivery system, cancer therapy, vaccine delivery, Cell culture technology, ocular as well as otic drug delivery system, intranasal drug delivery, parenteral drug delivery and pulmonary delivery of drugs as well as intranasal drug delivery system[27,28].

1.Improves water solubility of poorly water soluble drug

The Self Nanoemulsifying Drug Delivery System (SNEDDS) is important to improve water solubility of poorly water soluble drug and increases oral bioavailability of poorly water soluble drug.Hence such formulations has more importance to increases oral delivery of poorly soluble drug.

2.Protection against biodegradation

SNEDDS has important ability to deliver macromolecules like peptides, hormones, enzyme substrates are inhibitors and it is important to protect from enzymatic degradation.

CONCLUSION:

Recent newer drug discovery programs resulted in development of new therapeutic agents that are lipophilic and poorly soluble. Self nanoemulsifying drug delivery system showed tremendous potential in

improving the bioavailability of such drugs with limited aqueous solubility. The nanosize of these formulations are responsible for facilitating enhancement of drug dissolution and absorption, and provides large surface area. The lipidic nature of these systems helps in delivery of drugs to the lymphatic system. However, certain issues like drug-excipient interactions, oxidation of vegetable oils, toxicity and safety warrant attention during the development of SNEDDS should be given keen attention. The amenability of converting the liquid SNEDD into solid SNEDD enables its development into a solid dosage form. Thus, the solid self-nanoemulsifying system would serve as platform technology in the delivery of poorly soluble drugs. Although a lot of research is being carried out in this area, other aspects like *in vitro-in vivo* correlation, need to be established [26-28].

Self Nanoemulsifying drug delivery system (SNEDDS) is a novel approach for the formulation of drug molecules with poor water solubility. Self Nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of oils, surfactants, cosurfactant (Smix) and co-solvents. When introduced into aqueous phase, it emulsifies spontaneously to produce fine O/W nanoemulsion under gentle agitation. SNEDDS is a good alternative for the formulation of poorly water soluble drugs. SNEDDS improves the dissolution of the drugs due to increased surface area on dispersion and absorption rate of drug molecule. The oral delivery of lipophilic drugs can be made possible by SNEDDS, is important to improve oral bioavailability. According to this approach it is possible to prolong the release of drug via incorporation of polymer in composition. SNEDDS seems to be appear as unique and industrially survival approach with future development.

SNEDDS are a promising approach for drugs that comes under BCS class II or IV 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 advancements in this technology, SNEDDS will continue to enable its novel applications in drug delivery and therby helps to solve problems associated with the delivery of poorly soluble drugs, mainly BCS class II and IV drugs.

Future Perspective

Research on SNEDDS technology has accelerated in the last few years and several reports on primary exploration of SNEDDS for the enhancement of oral bioavailability have appeared in the literature. Factrors like pH catalyzed and solution state degradation of drugs in SNEDDS needs to be evaluated. The conversion of liquid SNEDDS to a solid state such as granules, tablets , capsules or pellets with no or moderate effects on the *in vivo* behavior of SNEDDS can reduce the chances of drug degradation as it may not be fruitfull in many cases. Thus, it is important to identify microenvironment modulation strategies employed for improving the stability of pH sensitive drugs. It may also be possible to develop controlled release SNEDDS by suitable variations in the composition or fabrication process of tablets or granules. However, it is also necessary to identify a potential highly porous amphiphilic carrier that can convert liquid SNEDDS into a solid powder without causing any significant increase in the volume or bulk density. The applications of SNEDDS in other routes of delivery apart from the oral route should also be needed to explored. Thus ,the commercialization of SNEDDS would be a breakthrough in the drug delivery.

REFERENCES:

1.Ali MN, Ahmed RG, Hassan MG, Mamdouh MG. Design, formulation and *in-vitro* characterization of Irbesartan solid self-nanoemulsifying drug delivery system (S-SNEDDS) prepared using spray drying technique. Journal of Chemical and Pharmaceutical Research. 2016; 8(2):159-183.

2.Khade S, Pore Y. Formulation and Evaluation of Neusilin Us2 Adsorbed Amorphous Solid Self micro emulsifying Delivery System of Atorvastatin Calcium. Asian Journal of Pharmaceutical and Clinical Research. 2016; 9(4): 1-8.

3.Rajendra ND, Mohammed H, Touseef H,Devi R. Design, optimization and evaluation of glipizide solid self-nanoemulsifying drug delivery for enhanced solubility and dissolution. Saudi Pharmaceutical Journal. 2015; 23: 528–540

4.Sunitha RM; Sowjanya N. Formulation and *in-vitro* Characterization of Solid Self Nanoemulsifying Drug Delivery System (s-SNEDDS) Of Simvastatin. J. Pharm. Sci. & Res. 2015; 7(1): 40-48.

5.Narkhede RS, Gujar KN, Gambhire VM. Design and Evaluation of Self Nanoemulsifying Drug Delivery Systems for Nebivolol Hydrochloride. Asian Journal of Pharmaceutics. 2014; 200-9.

6.Forgiarini A, Esquena J, Gonzalez C, Solans C . Formation of nano-emulsions by low-energy emulsification methods at constant temperature. Langmuir. 2001; 17: 2076-2083

7.Pouton CW, Porter CJ. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Adv. Drug Deliv. Rev. 2008; 60(6):625–637.
8.Lundin P, Bojrup M, Ljusberg-Wahren H, Westrom B, Lundin S. Enhancing effects of monohexanoin and two other medium-chain glyceride vehicles on intestinal absorption of desmopressin (dDAVP). *J.* Pharm. Exp. Ther. 1997; 282: 585–590.
9.Taha EI, AlSuwayeh SA, Anwer MK . Preparation, in vitro and in vivo evaluation of solidstate Self nanoemulsifying drug delivery system (SNEDDS) of vitamin A acetate. J. Drug Target. 2009; 17: 468–473.
10.Yoo JH, Shanmugam S, Thapa P et al.: Novel self-nanoemulsifying drug delivery system for enhanced solubility and dissolution of lutein. Arch. Pharm. Res. 2010; 33: 417–426 .
11.Mahmoud EA, Bendas ER, Mohamed MI: Effect of formulation parameters on the preparation of superporous hydrogel self-nanoemulsifying drug delivery system (SNEDDS) of carvedilol. AAPS Pharm. Sci. Tech. 2010; 11: 221–225.
12.Mahmoud EA, Bendas ER, Mohamed MI. Preparation and evaluation of self nanoemulsifying tablets of carvedilol. AAPS Pharm. Sci. Tech. 2009; 10: 183–192.
13.Wang Z, Sun J, Wang Y et al.: Solid selfemulsifying nitrendipine pellets: preparation and in vitro/in vivo evaluation. Int. J. Pharm. 2010;383: 1–6.
14.Yi T, Wan J, Xu H, Yang X. A new solid selfmicroemulsifying formulation prepared by spraydrying to improve the oral bioavailability of poorly water soluble drugs. Eur. J. Pharm. Biopharm. 2008; 70: 439–444.
15.Fatouros DG, Deen GR, Arleth L et al. Structural development of self nano emulsifying drug delivery systems (SNEDDS) during in vitro lipid digestion monitored by small angle Xray scattering. Pharm. Res. 2007; 24: 1844–1853.
16.Abdalla A, Mader K. Preparation and characterization of a selfemulsifying pellet formulation. Eur. J. Pharm. Biopharm. 2007;66: 220–226.
17.Fatouros DG, Mullertz A. In vitro lipid digestion models in design of drug delivery systems for enhancing oral bioavailability. Expert Opin. Drug Metab. Toxicol. 2008;4: 65–76.
18.Corveleyn S, Remon JP. Formulation of a lyophilized dry emulsion tablet for the delivery of poorly soluble drugs. Int. J. Pharm. 1998;166: 65–74.
19.Hyma P, Anusha C, Abbulu K. Formulation and Characterization of Telmisartan Self Microemulsifying Drug Delivery System. International Journal of Pharmacy and Pharmaceutical Sciences. 2014; 6(1): 120-5 .
20.Gurjeet K, Pankaj C, Harikumar SL. Formulation Development Of Self Nanoemulsifying Drug Delivery System (SNEDDS) Of Celecoxib For Improvement Of Oral Bioavailability. *Pharmacophore* 2013; 4 (4): 120-133.
21.Buyukozturk F, Benneyan JC, Carrier RL. Impact of emulsion based drug delivery systems on intestinal permeability and drug release kinetics. *J. Control Release.* 2010;142: 22–30.
22.Patil P, Paradkar A: Porous polystyrene beads as carriers for self emulsifying system containing loratadine. AAPS Pharm. Sci. Tech. 2006; 7(1): E28 .
23.Suvakanta D, Padala NM, Prasantha C. Review-Kinetic modelling on drug release from Controlled drug delivery system. Acta Poloniae Pharamaceutica. 2010; 67(3): 217-233
24.Patil PR, Biradar SV, Paradkar AR. Extended release felodipine self-nanoemulsifying system. AAPS Pharm. Sci. Tech. 2009;10(2): 515–523.
25.Nazzal S, Khan MA. Controlled release of a selfemulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. Int. J. Pharm. 2006; 315: 110–121.
26.Tuleu C, Newton M, Rose J et al. Comparative bioavailability study in dogs of a selfemulsifying formulation of progesterone presented in a pellet and liquid form compared with an aqueous suspension of Progesterone. J. Pharm. Sci. 2004; 93: 1495–1502.
27.Gursoy RN, Benita S. Self-emulsifying drug delivery systems (SEDDS) for improved oral delivery of lipophilic drugs. Biomed Pharmacother. 2004;58: 173.
28.Kawakami K, Yoshikawa T, Moroto Y, Kanaoka E, Takahashi K , Nishihara Y et al. Microemulsion formulation for enhanced absorption of poorly soluble drugs. I. Prescription design. J. Cont. Rel. 2002; 81: 65.