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REVIEW ARTICLE

Emerging formulation tool for drug delivery: Self nano-emulsifying drug delivery system (SNEDDS)

AKSHAY R YADAV*

Department of Pharmaceutical Chemistry, Rajarambapu College of Pharmacy, Kasegaon, Maharashtra, India-415404

***Author for Correspondence:** *Email:* akshayyadav24197@gmail.com

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ABSTRACT

Oral delivery of lipophilic drugs faces major challenges due to low aqueous solubility of such compounds. Self Nano-emulsifying drug delivery systems (SNEDDSs) have ability to increase solubility and bioavailability poorly soluble drugs. SNEDDS are isotropic mixtures of oils, surfactants, solvents and co-solvents/co-surfactants that can be used for the design of formulations in order to improve oral absorption of highly llipophilic drug compounds. The Self Nanoemulsifying Drug Delivery System (SNEDDS) is important application on BCS class II and class VI drugs for improving water solubility of poorly water soluble drugs and improve bioavailability. Various surfactants and oils were screened as candidates for SNEDDS on the basis of droplet size of resulting emulsions. This review offers an updated overview of SNEDDS application from the biopharmaceutical point of view.

INTRODUCTION

Self-Nano Emulsifying Drug Delivery System (SNEDDS) is defined as isotropic mixture of natural or synthetic oils, solid or liquid surfactants and co-surfactants. It has ability to forming fine oil-in-water (O/W) nanoemulsion under mild agitation followed by aqueous media [1]. SNEDDS having size range of globules is less than 100 nm under dispersion of water. The self Nanoemulsifying drug delivery system is thermodynamically stable and Transparent or Translucent Non-ionized dispersion of (o/w) and (w/o) nano emulsion was stabilized by addition of surfactant and co- surfactant molecule [2].

Mechanism of Self-Emulsification

According to Reiss, self-emulsification occurs when entropy changes that favours dispersion is greater than energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of energy required to create new surface between the oil and water phases and water phases and can be described by the equation. In emulsification process the free energy (ΔG) associated is given by the equation [3]:

$$\mathbf{\Delta G} = \Sigma\ (N\pi r2\sigma)$$

ΔG = the free energy associated with the process (ignoring the free energy of mixing); N = the number of droplets of radius r and s is the interfacial energy; r = the radius of globules;
σ = the interfacial energy.

The two formed phases of the emulsion will tend to separate with time to reduce the interfacial energy and thus reduce free energy of the system. The conventional emulsifying agents stabilize emulsions, reduce the interfacial energy by forming a monolayer around the emulsion droplets, and in turn, provide a barrier to coalescence [4].

Advantages and Disadvantages of SNEDDS

Advantages

- **Improvement in oral bioavailability**

Dissolution rate dependent absorption is major factor that limits the bioavailability of poorly

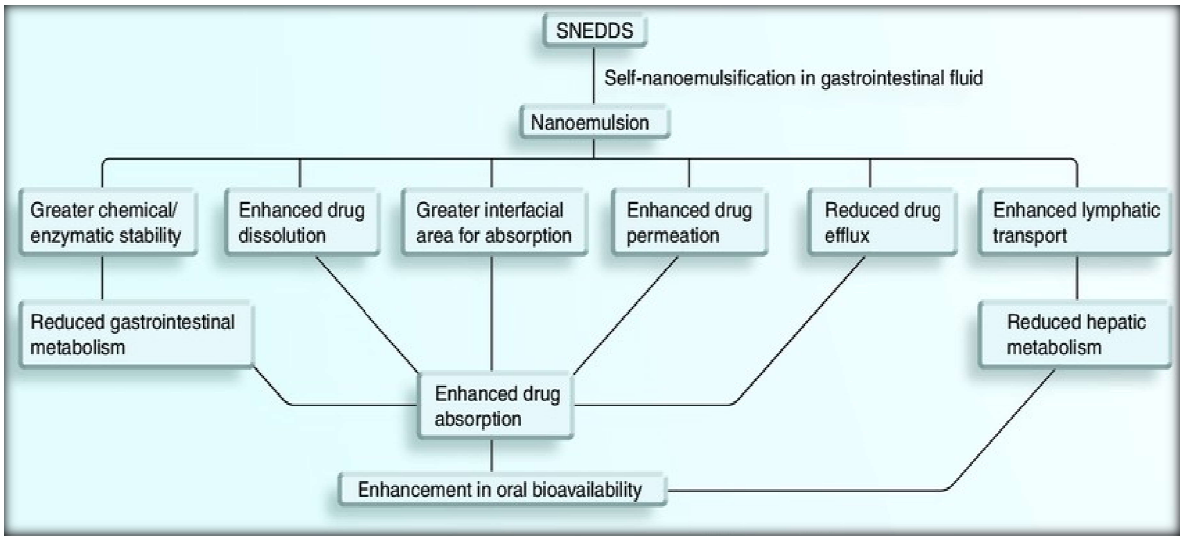

Figure 1: Potential mechanism of SNEDDS to enhancing bioavailability

water soluble drugs. The ability of SNEDDS to present the drug to get in solubilised and nanoemulsified form and subsequent increase in specific area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability [5].

- **Long-term colloidal stability**

Nanoemulsions can have long-term colloidal stability when fabricated using optimum conditions. Owing to this property, nanoemulsions can be used as drug carriers and can impart long shelf-life to the pharmaceutical product.

- **Ability to solubilise hydrophilic and hydrophobic therapeutic agents**

Nanoemulsions have the ability to solubilize hydrophobic as well as hydrophilic drugs in their nanostructure depending on the type of nanoemulsion. The O/W nanoemulsions are used for improving delivery of hydrophobic drugs, whereas W/O nanoemulsions are preferred for incorporating hydrophilic drugs [6].

- **Patient compliance**

The SNEDDS formulations can be filled into unit dosage forms, such as soft/hard gelatin capsules, which improves patient acceptability and commercial viability.

- **Palatability**

No palatability-related issues in comparison with other formulations /tablets, as SNEDDS formulations can be filled into capsules.

- **Reduction in drug dose**

SNEDDS offer improved drug-loading capacity and oral bioavailability or therapeutic effect for numerous hydrophobic drugs owing to the drug solubility in excipients. The enhancement in drug-loading and bioavailability can be translated into reduction in the drug dose and dose-related side effects of many hydrophobic drugs [7, 8].

- **Ease of manufacture and scale up**

Ease of manufacture and scale-up are key factors that govern success in its industrial applicability. The methods employed for the fabrication of SNEDDS formulations, such as simple mixed with an agitator and volumetric liquid filling equipment, offer easy manufacture at large-scale and economic benefits as well.

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

There are several drugs, such as cyclosporine and ezetimibe that show large inter- and intra-subject variation in absorption leading to decreased performance of the drug and patient noncompliance. It has been demonstrated that fed and fasted state dissolution media have negligible effects on the droplet size of the SNEDDS. Hence, it can be anticipated that SNEDDS (fabricated with proper optimization) can offer a reduction in ratio of bioavailability between fed and fasted state and can offer reproducibility in plasma profiles of drugs in fed and fasted conditions [9].

Disadvantages

Traditional dissolution methods do not work, because these formulations potentially

are depend on digestion prior to release of the drug.

i. This *in vitro* model needs further development and validation before its strength can be evaluated.
ii. The drawbacks of this system include chemical instabilities of drug and high surfactant concentration in formulations (approximately 30-60 %) which irritates the gastrointestinal track.
iii. Sometimes co-solvent remains into the formulation and cause degradation of drugs.
iv. It may allow less drug loading.
v. Formulations containing several components become more challenging to validate [10].

Drug Properties Suitable for SNEDDS

a) Dose of drug should not be high.
b) Drug should be oil soluble.
c) Melting point should not be high.

Lipid based compound forms a potential platform for improving oral bioavailability of drug especially those belonging to BCS Class II and IV. An important indication of the potential utility of lipid based formulation can be obtained by accessing drug lipophilicity (Log P) and its solubility in pharmaceutically accepted lipid excipients. Another indicator of potential success of lipid based formulation is the observance of strong positive food effect when the drug is administered with fatty meal as opposed to dosing in the fasting SMEDDS usually provide advantage of increased drug loading capacity as the solubility of poorly water soluble drugs with intermediate partition coefficient (2<Log P <4) are typically low in natural lipid and much greater in surfactant, co-surfactant [11].

Excipients Selection for Lipid Based Formulations

Chemically, lipids are considered as one of the most versatile excipient class available today. There are various subcategories of lipids available and there is a constant influx of new lipid based excipients in the market. This provides flexibility to the formulator in terms of selecting a suitable excipient, but at the same time, the formulator should be cautious while selecting a particular excipient. These are few factors that should be considered while selecting a lipid excipient. They are:

a) Regulatory issues
b) Solvent capacity
c) Morphology at room temperature
d) Self dispersibility
e) Miscibility
f) Digestibility and fate of digested products
g) Capsule compatability
h) Chemical stability, purity and cost.

Composition of SNEDDS

A. Oil
B. Surfactant
C. Co-surfactant
D. Drug
E. Other components

A. Oil:

The oil is important for maximum solubilizing ability for selected drug candidate is important for selection of oily phase for Nanoemulsion Formulation. This is most important approach having the high drug loading ability. The naturally as well as synthetically occurring the mixture of oils and fats are triglycerides contain in long chain fatty acids. The Triglycerides are classified as short chain Triglycerides (<5 carbons), medium chain Triglycerides (6-12 carbons atoms), or long chain Triglyceride (>12 carbons) is important to decrease the degree of unsaturation and is important to prevent oxidative degradation. The choice of oily phase is depends on the ability of the solubilized drugs and it is important to from nanoemulsion of desired characteristics. The oil is important to increases friction to transport of drug into intracellular compartment is important to increases water solubility of less water soluble drug. The long chain and medium chain triglyceride oils under different degrees of saturation is important to use in designing of SNEDDS. The medium chain triglycerides (MCT) molecules having higher solvent capacity and ability for resistance to oxidation as compare to long chain triglycerides molecules. Now days, the MCT have been replaced by novel semi-synthetic MCT is important to influencing 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, hydrogenated oil for better solubility [11, 12].

B. Surfactant

The choice of surfactant plays a significant role in SNEDDS. Surfactant are define as molecules and ions are adsorbed at interface i.e. surfactant. It is having ability to prevent the interfacial tension and provide interfacial area. It is major component for preparation of nanoemulsion. A

surfactant is amphiphilic agent having two parts with different affinities for the solvents and the two parts are polar head group region and non-polar tail region. Surfactant is widely used for industrial, agriculture, foods, cosmetics and pharmaceutical application such as solubilizing, emulsifying and enhancing agent.

Surfactants are classified in four different classes like,

a) Anionic surfactant
b) Cationic surfactant
c) Non-ionic surfactant
d) Zwitterionic surfactant

Surfactant is worked on the mechanism that is, inference of lipid bilayer of epithelial membrane with unstirred aqueous layer, forming the rate limiting barrier to drug absorption or diffusion and that inhibit the Cytocrome P450. There is several compounds having the surfactant property but the limited surfactants are orally accepted. The most commonly used Surfactants are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene 20 oleate. Optimum amount of surfactant unit is used for preparation nanoemulsion but large quantity of surfactant can chemical toxicity. Hence the safety is major considerable parameter for selection of Surfactant molecule. The Non-ionic surfactant having more stable as compared to Ionic surfactant molecule and they are nontoxic and Thermodynamically Stable Molecule. Surfactant is used in these formulation to increase bioavailability, this include different mechanism like enhanced drug dissolution in the gastrointestinal fluid, especially in the presence of bile salt, lecithin and lipid digestion mixtures, increased epithelial permeability, increased tight junction permeability and inhibited P-glycoprotein drug efflux. This can avoid precipitation of the drug in the GI lumen and prolonged existence of the drug molecule. 20 to 50% of surfactant concentration used in the formulation [13].

C. Co-surfactant

Co-surfactant is similar function to surfactant unit. Co-surfactant was added along with surfactant unit or combination of surfactant unit to able to increases the ability Surfactant to improving water solubility of poorly water soluble drug. The co-surfactant are Single chain Surfactant unit are able to Prevent the Interfacial Fluidity. The co-surfactant molecule is come into contact with surfactant, oil and water it can 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 co-surfactant in self Nanoemulsifying Drug Delivery system (SNEDDS) is to prevent interfacial tension between oil and water interface. Co-surfactant like Ethanol, Methanol, Pentanol, Glycol, Propylene Glycol etc [14].

D. Drug:

Drug is most important part of the formulations. Drug must be soluble in oil phase as this affect the ability of SNEDDS to maintain the drug in solubilized form. Drug having very high dose and low solubility in oil are not suitable for the SNEDDS formulation. High melting point drugs with log P value of about 2 are poorly suitable for SNEDDS. While lipophilic drug having log P value more than 5 are good candidate for SNEDDS.

E. Other components:

a) Enzyme Inhibitors:

If the therapeutic agent is subject to enzymatic degradation, enzyme inhibitors can be added to the composition of SNEDDS.

Enzymes inhibitors are:
Inhibitors that are not based on amino acids, e.g. P-aminobenzamide, Sodium Glycocolate. Amino acids and modified amino acids, e.g. aminoboronine derivatives and n-acetylcycteine. Peptides and modified peptides e.g. bacitracin and amastatin. Polypeptide protease inhibitors
e.g. Apratinin, soyabean trypsin inhibitor, chicken egg white trypsin inhibitor.

b) Consistency Builder:

Complexing agent
e.g. EDTA, EGTA, Phenanthroline, Hydroxychinoline.

c) Polymers:

Inert polymer matrix representing from 5 to 40% of composition relative to the weight, which is not ionisable at physiological pH and being capable of forming matrix are used for the Formulation of sustained release SMEDDS. The polymer matrix after ingestion, in contact with GI fluid, forms a gelled polymer making it possible to release the micro emulsified active agent in a continuous and sustained manner by diffusion [15].

❖ **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 or Phase inversion method. The procedure consisted of preparing solutions Containing oil and the different ratio of surfactant to co-surfactant by weight such as 1:1, 2; 1, 3:1 etc., these solutions then vortexed for 5 min and isotropic mixture was obtained. Observed for their appearance (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) Percentage of oil, Smix and water. The Pseudoternary phase diagram is represent mixture of surfactant, co-surfactant, oil, and water phase is shown in Fig. 2 [16].

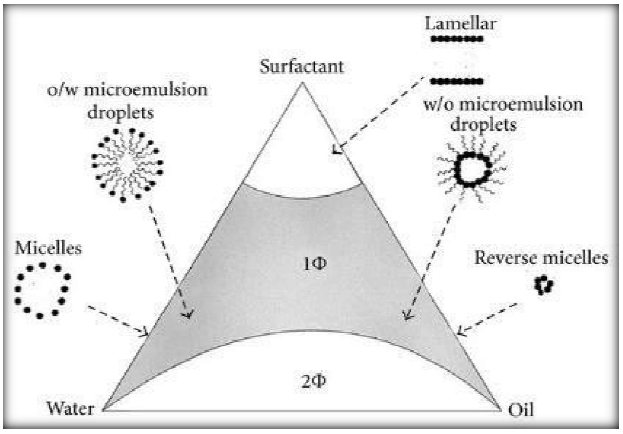

Figure 2: Diagram showing different regions of pseudo-ternary phase diagram

❖ **Evaluation of Self Nanoemulsifying Drug Delivery System (SNEDDS)**

➢ **Thermodynamic stability of emulsion**

Use to study the precipitation of the drug in the excipients matrix. If there is poor formulation Thermodynamic stability can lead phase separation of the excipients affecting not only formulation performance as well as visual performance.

➢ **Centrifugation study**

The formulations were centrifuged and the resultant formulations were then checked for any instability problem, such as phase separation, creaming or cracking. Formulation which is stable selected for further studies [8].

➢ **Heating and cooling cycle**

There are three heating/cooling cycles between 4°C and 40°C with storage at each temperature for not less than 24h. The resultant formulations were assessed for their Thermodynamic instability like phase separation and precipitation. Formulation which passes this test subjected for further test.

➢ **Freeze thaw cycle**

Freeze thawing was employed to evaluate the stability of SNEDDS. 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 min. The formulations were then observed for phase separation [17].

➢ **Droplet size**

This is a crucial factor in self-emulsification performance because it determines the rate and extent of drug release as well as the stability of the emulsion. 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 1000HS (Malvern Instruments, UK). Light scattering was monitored at 25 °C at a 90° angle. The optimized nanoemulsion sample was diluted by distilled water, placed in quartz corvette and subjected to droplet size analysis.

➢ **Viscosity**

The Viscosity (rheological property) of the self-nanoemulsifying drug delivery system (SNEDDS) was evaluated by Brookfield Viscometer for Determination of Consistency of Nanoemulsion Formulation.

➢ **Determination of emulsification time**

Self-emulsification time, dispersibility, appearance and flowability were observed and Score according to techniques used for the grading of formulations.

➢ **Drug content**

It is important for determination of percent content of drug product as well as percent purity of Nanoemulsion system. By using absorption method drug content is determined [18].

❖ **Conversion of liquid SNEDDS in to Solid SNEDDS**

Transformation of SNEDDS into solid dosage form has been extensively investigated in the recent years because solid dosage forms improve stability, handling and patient compliance. By

using different solidification techniques self-emulsifying powders, granules, pellets and tablets can be produced. Appropriate excipients, solid carriers and processing parameters must be selected for each solidification technique to enable processability and preserve the self-emulsifying ability of the system upon its transformation into the solid formulation. Liquid SNEDDS can be filled in soft or hard gelatine capsule. Recently, there have been efforts by research groups working on to convert liquid SNEDDS to solid state SNEDDS. These Solid SNEDDS can be made into tables or be encapsulated [18-21].

- Oral solid dosage form has following advantages:
- ✓ Low product cost
- ✓ Convenience of process control
- ✓ High stability and reproducibility and
- ✓ Better patient compliance

Generally, the formulated SNEDDS are liquid in state, but sometimes it could be in a semisolid state depending on the physical state of excipients used. Researchers have adopted various techniques to obtain this conversion. Solid SNEDDS also offers added versatility in terms of possible dosage forms.

❖ Solidification Techniques for Transforming Liquid SNEDDS to S-SNEDDS

➢ Adsorption to solid carriers:

Adsorption to solid carriers, which have high porosity and/or high specific area, is recently the most intensively investigated approach to obtain solid lipid formulations, dry emulsions and solid SNEDDS. Often used carriers for adsorption of liquid SEDDS are: silicon dioxide; e.g. fumed silica under trade name Aerosil® with different grades of specific surface or micronized amorphous silica under trade name Sylysia® with different grades of pore volume; (II) magnesium aluminometasilicate under trade name Neusilin® with different surface properties (alkaline or neutral) and particle size, (III) calcium silicate and (IV) porous dibasic calcium phosphate anhydrous (e.g. Fujicalin®). Benefits of this solidification method are absence of organic solvents and a small number of excipients needed for final formulation. Technique also uses basic equipment and formulates free- flowing powders that can be filled into capsules or directly compressed into tablet with the aid of suitable excipients [22].

➢ Extrusion/Spheronization:

Extrusion/spheronization is one of the pelletization techniques used in pharmaceutical industry and also the most investigated method for self-emulsifying pellet production. Extrusion is a procedure of converting a raw material with plastic properties into cylinder- shaped agglomerate with uniform density. It is followed by spheronization where the extrudate is broken and formed into round pellets. Extrusion/spheronization yields spherical pellets with a narrow particle size distribution, good flow properties and low friability. The formation of the self-emulsifying pellets greatly depends on the pellet composition. A compromise between the smallest amount of adsorbent material needed and the largest amount of liquid SEDDS required is essential to produce pellets with good physical characteristics and highest possible drug loading.

➢ Wet Granulation:

Different carriers were used to prepare granulates. Generally, granulation process did not affect droplet size of nanoemulsion formed upon redispersing and drug release was higher than of bulk drug. Nonetheless, granulating with Microemulsion produces particles with broader size distribution and aggregation process is more difficult to control when compared with granulation where water is used as a granulating liquid.

➢ Spray Drying:

It is a promising technique for solidification of SEDDS and their further processing into tablets. Production of solid SEDDS by spray drying is possible with different carriers, whether hydrophilic or hydrophobic. The choice of carrier can affect drug release and oral bioavailability of drug incorporated by impacting the efficiency of SEDDS entrapment, as well as droplet size of (micro/nano) emulsion formed and reconstitution. disadvantage of solidification by spray-drying method could be lower yield due to the removal of non- encapsulated free drug with the exhausted gas Process yield (effectiveness of SEDDS entrapment) depends on the type of the carrier used. HPMC, Maltodextrin and lactose were used extensively in pharmaceutical industries as a carrier for solidification by means of spray drying.

➢ Melt Granulation:

Melt granulation is a process in which powder agglomeration is obtained through the addition

of a binder that melts or softens at relatively low temperatures. As a 'one step' operation, melt granulation offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover, it is also a good alternative to the use of solvent. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder. A wide range of solid and semisolid lipids can be applied as meltable binders. Thereinto, Gelucire®, a family of vehicles derived from the mixtures of mono-/di-/tri- glycerides and polyethylene glycols (PEG) esters of fatty acids [23-24].

CONCLUSION

The solubility of orally administered drugs is a major challenge for the pharmaceutical industry, as approximately 35-40% of newly released drugs have low aqueous solubility, resulting in poor dissolution and low bioavailability, resulting in high variability in intra-and inter-subjects and lack of proportionality of the dosage. Various techniques such as salt formation, solid dispersion and complex formation can increase this. To increase the solubility of lipophilic drugs, the Self-Emulsifying Drug Delivery System (SEDDS) is gaining popularity. Isotropic mixtures of one or more hydrophilic solvents and co-solvents/surfactants, with a remarkable ability to form fine oil-in-water (o/w) micro emulsions, following mild agitation and dilution in aqueous media, such as GI fluids. For drugs with low aqueous solubility, SEDDS is a promising solution and can also be more useful for BCS Class II and IV drugs than when administered. The SEDDS system takes water from its surrounding atmosphere when the dosage type reaches G.I.T and spontaneously forms oil in the water emulsion that disperses into fine droplets. The finer droplets provide the drug with a large surface area for dissolving or permeating in the surrounding medium. SEDDS are typically prepared in liquid dosage forms, but due to ease of handling, transportation and improved stability, solid SEDDS (tablets, capsules, beads, microspheres, etc.) are preferred.

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