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# **Self-Nano Emulsifying Drug-Delivery Systems: From the Development to The Current Applications and Update of the Biopharmaceutical Aspect**

**Sheetal S Buddhadev<sup>1\*</sup>, Kevin C Garala<sup>2</sup>**

**<sup>1</sup> Research Scholar, School of Pharmaceutical Sciences, Atmiya University, India.**

**Assistant Professor, Noble Pharmacy College, Junagadh, India**

**<sup>2</sup> Associate Professor, School of Pharmaceutical Sciences, Atmiya University, India.**

**\* Correspondence: [sheetal.buddhadev@ngivbt.edu.in](mailto:sheetal.buddhadev@ngivbt.edu.in)**



# ABSTRACT

Approximately one third of newly discovered drug molecules show insufficient water solubility and therefore low oral bioavailability. Different lipid-based formulations have been explored in the past few decades to improve the oral delivery of such compounds. Self-Nano emulsifying drug delivery systems (SNEDDS) are one of the emerging strategies developed to tackle the issues associated with their oral delivery.

Self-Nano emulsifying drug delivery systems (SNEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. The efficiency of oral absorption of said drug from such type of formulation depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. With the growing interest in this field, there is an increasing need for selection of excipients guidelines to obtain effective and safe delivery system with improved bioavailability. The aim of this review is to present mechanism of self-emulsification, composition, role of various excipients, formulation approaches, different techniques, evaluation parameters, factors affecting SNEDDS, Biopharmaceutical aspects and future perspective.

**Keywords:** Oral bioavailability; Self-Nano Emulsifying Drug Delivery Systems (SNEDDS), lipid formulation classification system (LFCS).

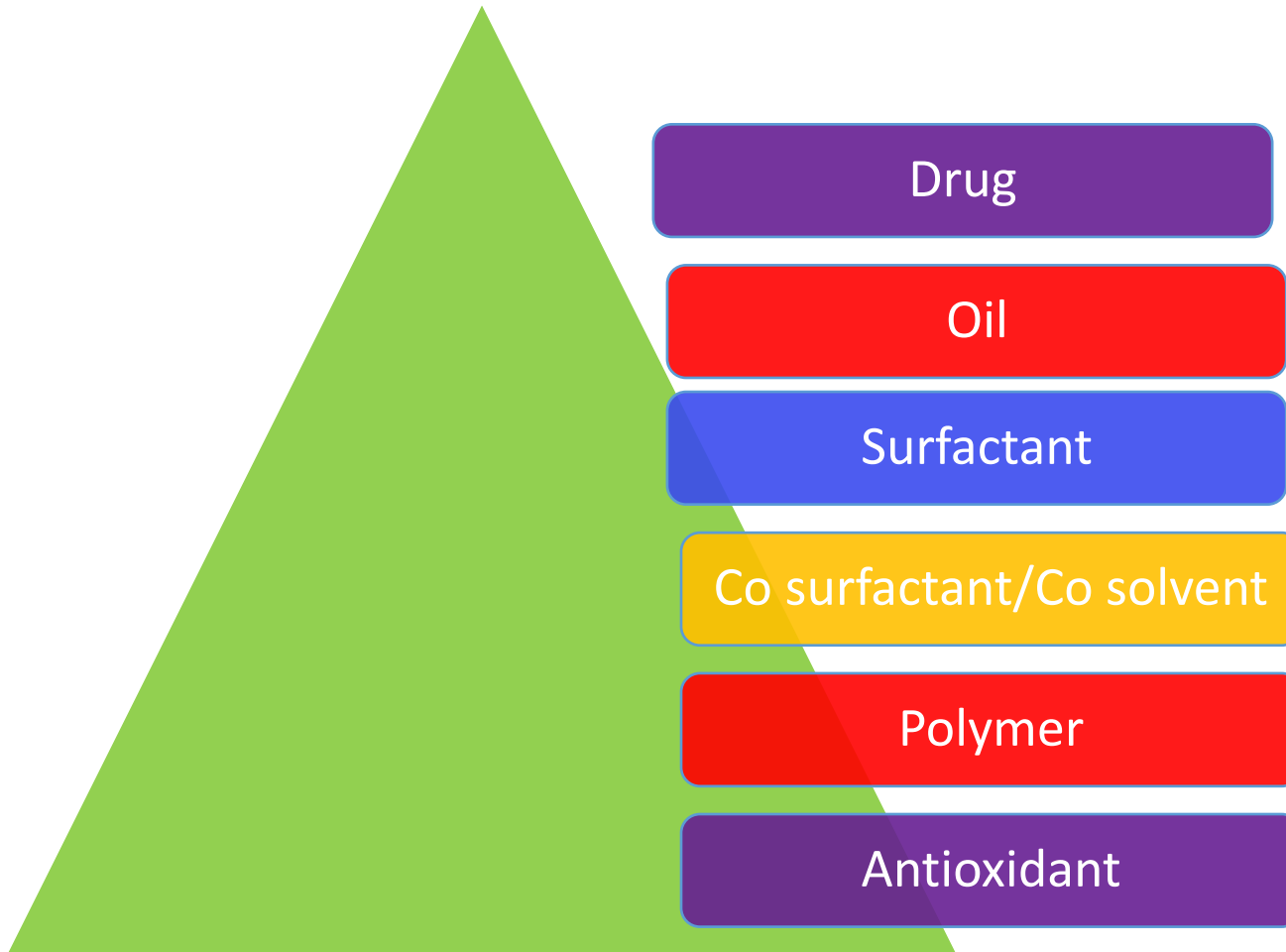
# INTRODUCTION<sub>(1-3)</sub>

- Oral route is considered to be the most convenient and preferred route for the patient among the various routes of drug delivery system.
- Solubility is one of the key determinants of oral bioavailability of a drug because a drug substance has to dissolve in the aqueous environment of the GI tract before it could be absorbed.
- The oral delivery of lipophilic drug estimated to be 40% of all new chemical entities identified in drug discovery Programs i.e. BCS Class II Drugs presents the greatest challenge for their poor aqueous solubility.
- Due to poor aqueous solubility, many drug candidates become unsuccessful to reach market in spite of exhibiting potential pharmacodynamic activity.
- Therefore, many strategies have been worked out improve the aqueous solubility as well as release rate of such drug from dosage forms.
- SNEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/ surfactants.

# INTRODUCTION<sub>(1-3)</sub>

- When SNEDDS formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/nano) so called as in situ emulsification or self-emulsification
- The self-emulsification process is specific to the particular pair of oil and surfactant, surfactant concentration, oil/surfactant ratio, and the temperature at which self-emulsification occurs.
- SNEDDS may enhance bioavailability via a number of potential mechanisms.
- Lipidic components of SNEDDS stimulate lipoprotein/chylomicron production thus promoting drug absorption.
- Stimulation of the intestinal lymphatic pathway as well as inhibition of intestinal drug efflux pumps such as P-glycoprotein (P-gp) and intestinal cytochrome P450 3A4.
- SNEDDS are considered promising strategies for enhancing the oral delivery of substance and bypassing intestinal and hepatic first pass metabolism .

# COMPOSITION OF SNEDDS (4)



## COMPOSITION OF SNEDDS (4)

### Drug:

- As, SNEDDS are used to increase the solubility of poor water-soluble drugs, BCS class II drugs are preferred.
- Drugs which are administered in very high dose are not suitable for formulation unless they have extremely good solubility in at least one of the components of SNEDDS, preferably oil phase.
- High melting point drugs with log P values of about 2 are poorly suitable for SNEDDS.
- Lipophilic drugs having log P values greater than 5, are good candidate for SNEDDS.
- Drugs which have low solubility in water or lipids are difficult to deliver through SNEDDS

## COMPOSITION OF SNEDDS (4)

### Oil:-

- Oils can solubilize the required dose of the lipophilic drug and facilitate self-emulsification.
- Natural edible oils remain the logical and desired oil ingredients, but they show relatively low drug-loading capacity and poor emulsification efficiency.
- Modified medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) are mostly employed to enhance the drug solubility in the formulation.
- MCTs are preferred because of their better solubilizing ability and self-emulsification capacity as well as increase the drug transport through the portal vein, but they have a limited capacity to enhance the lymphatic transport of the drugs.
- Conversely, LCTs are bypassing the hepatic first-pass metabolism and increase the transport of drugs through lymph vessel.
- Thus, a mixture of MCTs and LCTs can be considered to meet optimum properties and improve pharmacokinetics.

## Surfactants:

- Surfactant will improve bioavailability by different mechanism
  - ❖ Improve drug dissolution
  - ❖ Increase intestinal epithelial permeability
  - ❖ Increase tight junction permeability
- Different groups of surfactant can be applied for the Nano emulsion stability and formulating of SNEDDS: (i) ionic(ii) cationic (iii) anionic (iv) zwitterionic (v) nonionic.
- The most widely used are the non-ionic surfactants with a relatively high HLB.
- Natural surfactant have limited ability to emulsify.
- Usually, a stable SNEDDS formulation requires concentration 30% - 60% w/w. However; high concentration of surfactant may cause irritation to the gastric mucosa. Hence the safety is major considerable parameter for selection of Surfactant molecule.
- The selection of a particular surfactant for formulation depends upon its HLB value and safety issue.



# COMPOSITION OF SNEDDS (4)

## Cosurfactant:

- Co surfactant is similar function to surfactant unit. Co-surfactant was added along with surfactant unit to increases the ability of Surfactant to improving water solubility of poorly water-soluble drug.
- The co-surfactant is able to Prevent the Interfacial Fluidity.
- Allow interfacial film sufficient flexibility and reduces the overall effect of surfactant.

## Cosolvent:

- Medium chain alcohol C3-C8 are preferred, which increase fluidity of interface and entropy of the system.
- Commonly used Co solvent: Ethanol, Propylene glycol (PG), Polyethylene glycol (PEG), Glycerin, Polyoxyethylene.
- The newer cosolvents like Transcutol™ and Glycofurol™ have numerous advantages over the traditional ones, including better stability and less volatility.

# COMPOSITION OF SNEDDS (4)

## ➤ Viscosity Enhancers

The viscosity of the emulsions can be altered by the use of additional material such as acetyl alcohol, tragacanth, beeswax and stearic acids etc.

## ➤ Antioxidant agents

Lipophilic antioxidants E.g. alpha tocopherol, Propyl gallate, Ascorbic palmitate stabilize the oily content of SNEDDS formulation.

## ➤ Polymers

Polymer matrix (inert) present in 5 to 40 % w/w, which is not ionizable at physiological pH are able to form matrix.

Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

## MECHANISM (5)

- According to Reiss, Self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion.
- The interface between the oil and aqueous phases is formed upon addition of a binary mixture. This is followed by the solubilization of water within the oil phases as a result of aqueous penetration through the interface.
- The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water phases. In emulsification process the free energy ( $\Delta G$ ) associated is given by the equation.

$$\Delta G = \sum N \pi r^2 \sigma$$

where,

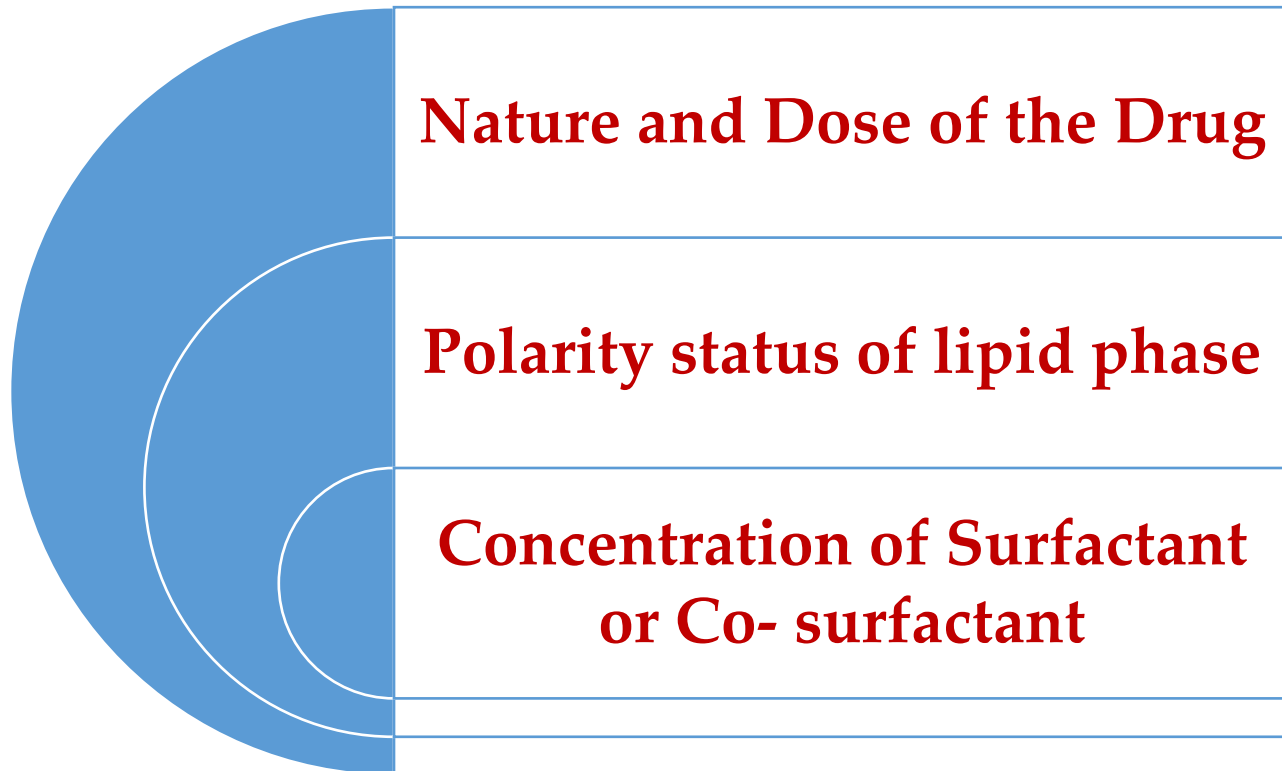
$\Delta G$  = free energy associated with the process

$N$  = number of droplets

$r$  = Radius of droplets

$\sigma$  = interfacial energy

# FACTORS AFFECTING SNEDDS PERFORMANCE(6)



# METHOD OF PREPARATION OF SNEDDDS (7)

Solubility profile study for selection of oil



Drug excipient compatibility study



Preparation of series of SNEDDDS system containing drug with various concentration of oil and surfactant and co surfactant by using Ternary Diagram



Optimization of formulation on the basis of *in -vitro* self emulsification properties, Droplet size analysis, Stability study, Robustness to dilution upon addition to water under mild agitation condition and finally by using Stastical Experiment Design.

# CHARACTERIZATION OF SNEDDS FORMULATIONS(8)

- 
- **Thermodynamic Stability Studies**
  - **Dispersibility test**

- 
- **Morphology and Particle Size**
  - **Drug Content**
  - **Zeta Potential**

- 
- **Viscosity Measurement**
  - **Refractive Index (R.I.) and Percent Transmittance**
  - **Robustness to Dilution**

- 
- **Cloud Point Measurement:**
  - ***In-vitro* Diffusion Study**
  - ***In-vitro* Dissolution Technique**

## SOLID-SNEDDS(9)

- Despite the benefits provided by liquid SNEDDS, drawbacks such as drug/components precipitation when stored, interactions between the filling and the capsule shell, and formulation stability during storage are common issues faced by Liquid SNEDDS.
- The main strategy applied to overcome these challenges is to transform liquid SNEDDS into solid dosage SNEDDS formulations.
- It is assumed that the conversion of liquid SNEDDS to solid SNEDDS provides relatively lower production cost, better formulation stability, ease of handling, precise dosing, and, consequently, better patient compliance.
- Generally, the techniques employed to develop solid SNEDDSs include:
  - ❖ Adsorption onto inert carriers
  - ❖ Spray drying
  - ❖ Melt granulation
  - ❖ Extrusion-Spheronization

# BIOPHARMACEUTICAL ASPECTS FOR FORMULATION DESIGN (8)

- The efficiency of the formulation is case specific in most instances thus, composition of the formulation should be determined very carefully.
- Since a relatively high concentration of surfactants is generally employed in the SNEDDS formulation, toxicity of the surfactant being used should be taken into account.
- A systematic elucidation of the rationale may be achieved by a pre selecting excipients for their fatty acid make up, melt characteristics, HLB or emulsification properties and overall digestibility.
- Conducting binary screening with the preselected excipients for drug solubility, compatibility, stability, and dissolution/dispersion properties to identify one or more suitable systems for further studies.
- Identifying the formulation techniques suitable for the dosage form intended as well as confirming the *in vivo* performance of the chosen formulation system in appropriate animal models.
- Optimizing the compositions as per individual physicochemical properties and absorption processes of a drug.
- Thorough understanding of the spontaneous Nano emulsification process, physicochemical and biological properties of the components used for the fabrication of SNEDDS are important for successful formulation of SNEDDS.



# MARKETED FORMULATION OF SNEDDS (8)

Drug Name	Trade Name	Company	Dosage Form
Tretinoin	Vesanoid®	Roche	Soft Gelatin capsules(10mg)
Tipranavir	Aptivus®	Boehringer Ingelheim	Soft Gelatin capsules (250 mg)
Cyclosporine A	Gengraf®	Abbott	Hard Gelatin capsules (25,100mg)
	Sandimmune®	Novartis	Soft Gelatin capsules (25,50,100 mg)
Isotretinoin	Accutane®	Roche	Soft Gelatin capsules (10,20,40mg)
Lopinavir and Ritonavir	Kaletra®	Abbott	Soft Gelatin capsules Lopinavir 133.33mg and Ritonavir 33.3 mg
Saquinavir	Fortovase®	Roche	Soft gelatin capsule(200 mg)

# FUTURE PERSPECTIVE AND CONCLUSION

- The use of lipid-based formulations in general and SNEDDS in particular shows great potential in enhancing aqueous solubility, stability, oral absorption and minimizing inter/intra-patient dose variability.
- SNEDDS are prepared generally in liquid dosage forms but solid SNEDDS are preferred due to ease in handling, transportation and better stability.
- Further, with solid SNEDDS, compatibility and interaction studies between the excipients such as adsorbent, capsule shell and formulation components can be carried out in order to effectively harness its potential for the benefit of mankind.
- Despite the above-mentioned advancements and modifications in SNEDDS, there are still areas that need to be addressed to make SNEDDS commercially attractive. The priority of future research should be based on pharmacokinetic studies especially on human subjects.
- So, we can conclude that SNEDDS seems to be appear as unique and industrially survival approach with future development.

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A blue ballpoint pen is shown writing the words "Thank you" in a cursive script on a white notepad. The notepad is slightly tilted, and the pen is positioned at the end of the word "you". The background is a soft, light blue gradient.

*Thank you*