SELF NANO EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW


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ABSTRACT

Self nanoemulsifying drug delivery systems enhance the solubility of poorly water soluble drugs. It is an isotropic mixture of oil, surfactant, co-surfactant molecules, which spontaneously form o/w nanoemulsion upon dilution with water under gentle stirring. They are highly in quest due to their innumerable benefits like better portability, improved stability and bioavailability, they are having a size of globules less than 100 nm. The SNEDDS is an important application of BCS class II and class IV drugs for improving solubility of poorly water soluble drugs. It is important to prevent the interfacial tension and improve the dissolution as well as absorption rate of drug molecules. This review mainly focuses on the components, mechanism of self emulsification, preparation, characterization, and applications and future perspectives of SNEDDS.

KEYWORDS: Self-emulsifying system, Triglycerides, Surfactant, Pseudoternary phase, Droplet size.

INTRODUCTION

Self nanoemulsifying drug delivery system (SNEDDS) is an isotropic mixture of natural or synthetic oil, surfactant and co-surfactant that have a unique ability of forming fine oil-in-water (o/w) nanoemulsion under mild agitation followed by addition of aqueous medium.[1] It is an efficient, elegant and more patient compliant formulation approach for poorly water soluble drugs. Self nanoemulsifying drug delivery system having a size of globules less than 100 nm under dispersion of water.[2] SNEDDS are characterized by high solvent capacity and excellent stability. In addition, they can improve oral bioavailability through enhancing
permeation across the intestinal membrane, reduce or eliminate food effect, solubilization, droplet size reduction and improvement of drug dissolution.\textsuperscript{[3]} The SNEDDS is formulated by using medium chain triglyceride oils and nonionic surfactant, is important for oil ingestion.\textsuperscript{[4]} It is the stable nanoemulsion providing a large interfacial area for partitioning of drug between aqueous and oil phase. The SNEDDS is thermodynamically stable and transparent or translucent non-ionized dispersion of (o/w) and (w/o) nano emulsion which is stabilized by addition of surfactant and co-surfactant molecule.\textsuperscript{[5]} The SNEDDS is also known as Miniemulsion, Nanoemulsion, Ultrafine emulsion, submicron emulsion.\textsuperscript{[6]} The SNEDDS formulations, containing bioenhancers that contain certain type of surfactants such as Cremophor\textsuperscript{®}, Tween80\textsuperscript{®} and Labrasol\textsuperscript{®} are also reported to further improve the bioavailability of absorbed compounds by facilitating transcellular and paracellular absorption.\textsuperscript{[7]}

**Comparison between self microemulsifying drug delivery system (Smedds) and Self nanoemulsifying drug delivery system (snedds).\textsuperscript{[8-12]}**

<table>
<thead>
<tr>
<th>Smedds</th>
<th>Snedds</th>
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<tr>
<td>2. It is thermodynamically stable.</td>
<td>2. It is thermodynamically and kinetically stable.</td>
</tr>
<tr>
<td>3. Droplet size is 100-300nm.</td>
<td>3. Droplet size is less than 100nm.</td>
</tr>
<tr>
<td>4. It is turbid in nature and a large amount of energy is required for preparation as compared to nanoemulsion.</td>
<td>4. Less energy required for preparation.</td>
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<tr>
<td>5. It is optimized by a ternary phase diagram.</td>
<td>5. It is optimized by pseudoternary phase diagrams.</td>
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</tbody>
</table>

**Bcs class of drugs suitable for snedds**

It is a novel approach for enhancement of oral bioavailability of poorly water soluble drugs. In the Biopharmaceutical classification system (BCS), they contain 4 classes among them class II and class IV drugs having poor water solubility as compared to class I and class III. The class II and IV are under a self nanoemulsifying drug delivery system and it is important to prevent problems of enzymatic degradation associated with class I and class III drugs and improved solubility and bioavailability.\textsuperscript{[13]}
Mechanism
The Self nano-emulsification occurs when the entropy change that favours dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and the water phases and it can be described by the following equation.

$$
\Delta G = \sum_{i=1}^{\infty} N_i \pi r_i^2 \sigma
$$

Where,
- $\Delta G =$ free energy associated with the process,
- $N =$ number of droplets,
- $r =$ radius of droplets,
- $\sigma =$ interfacial energy.

The two phases of the emulsion tend to separate with time to reduce the interfacial area and subsequently, it is stabilized by emulsifying agents, which form a monolayer of emulsion droplets and hence reduce the interfacial energy as well as providing a barrier to prevent the coalescence. The specificity of surfactant combination required to allow spontaneous emulsification may be associated with a minimization of the phase inversion temperature, thereby increasing the ease of emulsion.$^{[14]}$
Advantages and Disadvantages of snedds\textsuperscript{[15-21]}\n
<table>
<thead>
<tr>
<th>Advantages</th>
<th>Disadvantages</th>
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<tbody>
<tr>
<td>1. Enhanced oral bioavailability enabling reduction in dose.</td>
<td>1. The preparation of nanoemulsion (snedds) is difficult because the high pressure homogenizer as well as ultrasonic equipment was available in recent years and the preparative method is expensive.</td>
</tr>
<tr>
<td>2. It is important to provide ultra-low interfacial tension and provide large o/w interfacial areas.</td>
<td>2. Lack of good predictive \textit{in vitro} models for assessment of formulation because traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of drug.</td>
</tr>
<tr>
<td>3. The ability of nanoemulsion (snedds) to dissolve lipophilic drugs, and their ability to protect drugs from hydrolysis and enzymatic degradation make them ideal vehicles for parenteral transport.</td>
<td>3. To mimic this, an \textit{in vitro} model simulating the digestive processes of duodenum has been developed.</td>
</tr>
<tr>
<td>4. It can be stored easily since it belongs to a thermodynamics stable system.</td>
<td>4. The stability of the self nanoemulsifying drug delivery system was affected by pH and temperature.</td>
</tr>
<tr>
<td>5. Selective targeting of drug(s) toward specific absorption window in GIT.</td>
<td></td>
</tr>
<tr>
<td>6. It is essential for oils and their main components have applications in medicine, food, beverages, cosmetics, fragrance, pharmaceutical industries, and ayurvedic and unani systems.</td>
<td></td>
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</tbody>
</table>

**Components of snedds**

It is very important to select and optimize the quantities of the SNEDDS components because their concentrations will influence the various characteristics of nanoemulsion, such as droplet size, polydispersity index, self nano emulsification time and \textit{in vitro} drug release. In general, the selection of the components based on their ability to solubilize the drug of interest and also on their ability to form spontaneous emulsion/nano emulsion. The various components are:

a) Oil  

b) Surfactant  

c) Co-surfactant  

d) Co-solvent
a) Oils
The oil represents one of the important excipients in SNEDDS formulation not only because it can solubilize the required dose of lipophilic drug or facilitate self-emulsification but also and mainly because it can increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract depending on the molecular nature of the triglyceride. The oil increases friction to transport drugs into the intracellular compartment, which is important to increase water solubility of lipophilic drugs. The naturally as well as synthetically occurring the mixture of oils and fats are triglycerides contained in long chain fatty acids. The triglycerides are classified as short chain triglycerides (<5 carbons), medium chain triglycerides 6-12 carbon atoms), or long chain triglycerides (>12 carbons); it is important to decrease the degree of unsaturation and to prevent oxidative degradation. For example, the mixture of fixed oil and medium chain triglycerides is to maintain appropriate balance between loading capacity of drug and emulsification or nano emulsification. Triglycerides are highly lipophilic oily molecules and solvent capacity of drugs is a common function of effective concentration in ester groups, the medium chain triglycerides molecules are having high resistance to oxidation and high solvent capacity as compared to long chain triglyceride molecules. Now days, the medium chain triglycerides are replaced by novel semi-synthetic MCT (medium chain triglycerides) for 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 oil, sesame oil, soybean oil, hydrogenated oil for better solubility.\textsuperscript{[22-25]}

b) Surfactant
Surfactants are defined as molecules and ions are adsorbed at interface, i.e., surfactant. It is having the ability to prevent the interfacial tension and provide an interfacial area. It has a great effect on the emulsification process, nano-emulsifying region and droplet size. Most of the compounds can exist as surfactants for designing or emulsifying systems. Mainly nonionic surfactants are having high hydrophilic and lipophilic balance (HLB) and they are more stable, non-toxic and thermodynamically stable molecules compared to ionic surfactant molecules.\textsuperscript{[26]} Optimum amount of surfactant unit is used, the large quantities of surfactant cause toxicity. Surfactants are screened based on the emulsifying ability and this is done by mixing oil and surfactants under warming conditions and then diluted with deionized water to form isotropic mixtures. Once equilibrium obtained, percentage transmittance can be checked using spectrophotometer and droplet size, polydispersity indices are measured by zetasizer.\textsuperscript{[27]}
Concentration of surfactant influences the droplet size of the emulsion. It is an important component for preparation and for improving the solubility of poorly water soluble drugs.[28]

- **Classification of surfactant molecules**[29]

Surfactant molecules are classified into four types:

1. Anionic surfactants
2. Cationic surfactants
3. Ampholytic surfactants
4. Non-ionic surfactants

**1. Anionic surfactants**
The hydrophilic group carries a negative charge is known as Anionic surfactant. They contain negatively charged group such as carboxyl (RCOO⁻), sulfonate (RSO₃⁻) or sulphate (ROSO₃⁻).

**Examples** – Potassium laurate, sodium lauryl sulphate (SLS).

**2. Cationic surfactants**
The hydrophilic group carries a positive charge is known as cationic surfactant.

**Example** – quaternary ammonium halide.

**3. Ampholytic surfactants/ Zwiter or Zwitterionic surfactants**
The surfactant unit consists of both positive as well as negative charges.

**Example**- sulfobetaines.

**4. Non-ionic surfactants**
The hydrophilic group carries no charge but derives its water solubility because it can contain strong polar functional groups such as hydroxyl or polyoxyethylene HO-(CH₂CH₂O)ₓ-H

**Examples**- Sorbitan esters (Spans), polysorbates (Tween 20).

c) **Co-surfactant**
Co-surfactants are used to improve emulsification of the surfactant. The co-surfactants are single chain surfactant units able to prevent the interfacial fluidity. The important application of co-surfactant in self nanoemulsifying drug delivery systems (SNEDDS) is to prevent interfacial tension between oil and water interface.[30] They are also screened by mixing various co-surfactants with selected surfactant and oily phase under warming conditions and then diluted with water to form isotropic mixtures. This will allow attaining equilibrium and then percentage transmittance, droplet size and polydispersity index must be measured. The co-surfactant molecules come into contact with surfactant, oil and water; it can be separated
by a monomolecular layer of surfactant molecules. The monomolecular layer of surfactant molecules is known as Liquid crystal formation layer.\[^{31}\]

e) Co-solvent

Co-solvent is important to prevent interfacial tension and provide a larger surface area. It is important to increase oral bioavailability of poorly water soluble drugs.\[^{32}\]

**Examples of components used in snedds**

<table>
<thead>
<tr>
<th>Components</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipids and oils</td>
<td>Fatty acids: Palmitic acid, Stearic acid, Oleic acid</td>
</tr>
<tr>
<td></td>
<td>Fatty acid and esters: Glyceryl monooleate, Glycerol monostearate, Glycerol monolinooleate, Glycerol palmito stearate, Glycerol behenate, Ascorbyl palmitate, Medium chain mono- and diglycerides, Medium chain triglycerides, Glycerol dilaurate, Propylene glycol monolaurate.</td>
</tr>
<tr>
<td></td>
<td>Propylene Glycol esters: Propylene Glycol monocaprylate, Propylene glycol dicaprylocaprate.</td>
</tr>
<tr>
<td></td>
<td>Miscellaneous: Stearyl alcohol, Phospholipids, Beeswax, Vitamin E</td>
</tr>
<tr>
<td>Surfactants/ stabilizers</td>
<td>Caprylocaproyl polyoxyxyl-8-glycerides, Polyoxyethylene sorbitan fatty acid esters [Tweens], Polyoxyethylene castor oil derivatives, Polyvinyl alcohol, Sorbitan esters [Spans], Tocopherol polyethylene glycol succinate (TPGS)</td>
</tr>
<tr>
<td></td>
<td>Macrogol fatty acid glycerides, Hydroxypropyl methylcellulose, Poloxamer, Phospholipids and PEGylated phospholipids, Polyvinyl pyrrolidone, Bile acids (sodium deoxycholate), Cellulose derivatives, Polyglyceryl-3 dioleate.</td>
</tr>
<tr>
<td>Co-surfactants /co-solubilizers /co-stabilizers</td>
<td>Propylene glycol, Glycofurol, Phospholipids, Oleoyl/linoleoyl polyoxyxyl-6-glycerides, Polyethylene glycol, Triacetin, ethanol, Diethylene glycol monoethyl ether.</td>
</tr>
</tbody>
</table>

Fig. 2: Formation of emulsion by the use of surfactant.
Methods for preparation of snedds

1. High pressure homogenizer

It is one of the important devices for preparation and detection of nanoemulsion. This method is performed by applying a high pressure over the system having oil phase, aqueous phase and surfactant or co-surfactant. The pressure is applied with the help of a homogenizer. During this process, several forces, such as hydraulic shear, intense turbulence and cavitation, act together to yield nanoemulsions with extremely small droplet size. The high velocity of mixture gives the liquid high energy in the homogenizer valve generates intense turbulent eddies of the same size as the mean diameter droplet (MDD). Droplets were apart from eddy 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, which is responsible for a greater degree of cavitation. [33]

Surfactant mixtures that show more reduction in surface tension than the individual components could also be used. If possible the surfactant is dissolved in the dispersed phase rather than the continuous phase; this often leads to small droplets. Some problems associated with homogenizer are poor productivity, component deterioration due to generation of much heat. With this method only oil in water (O/W) liquid nanoemulsion of less than 20% oil phase can be prepared and cream nanoemulsion of high viscosity or hardness with a mean droplet diameter lower than 200 nm cannot be prepared. [34]

2. Sonication method

In sonication method the droplet sizes of conventional emulsion or microemulsion are decreased with the help of sonication mechanism. This type of method is important for determination of the size of droplets and this method is not applicable for large batches, but only limited batches of nanoemulsion can be prepared by this method. [35]

3. Microfluidization

Microfluidization technology makes use of a device called “MICROFLUIDIZER”. This device uses a high pressure positive displacement pump (500-2000 PSI) which forces the product through the interaction chamber, consisting of small channels called micro channels. The product flows through the microchannels onto an impingement area resulting in very tiny particles of submicron range. [38] The two solutions (aqueous phase and the oily phase) are combined together and processed in an inline homogenizer to produce a coarse emulsion. The
coarse emulsion is passed into a microfluidizer where it is further processed to get a stable nanoemulsion. The coarse emulsion is passed through the interaction chamber microfluidizer repeatedly until required particle size is obtained. The bulk emulsion is then filtered through a filter under nitrogen to remove large droplets leading in a uniform, transparent, stable nanoemulsion.\textsuperscript{[36-37]}

4. Phase inversion method

The phase inversion method is important for preparation of nanoemulsion and microemulsion. The method is based on the response to temperature. Fine dispersions are obtained by chemical energy resulting from phase transitions occurring through emulsification methods. The adequate phase transitions are produced by changing the composition at constant temperature or by changing the temperature at constant composition. These methods make use of changing the spontaneous emulsion formation. The spontaneous emulsion formation of nonionic surfactant can be achieved by changing the temperature of the system; thus forcing a transition from o/w nanoemulsion formed at low temperature to w/o nanoemulsion at higher temperature.\textsuperscript{[38]}

5. Pseudoternary phase diagram

Pseudoternary phase diagram is important for determination of self nano emulsifying drug delivery system (SNEDDS). It was constructed by phase inversion and phase transition method. It is a diagrammatic representation of oil, water, surfactant and co-surfactant. The procedure consists of preparing solutions containing different ratios of surfactant to co-surfactant and oil by weight such as 1:1, 2:1, 3:1, these solutions then vortexed for 5 min and an isotropic mixture was obtained. Observed for their appearance (clear or turbid). Turbidity of the samples would indicate formation of a coarse emulsion, whereas clear isotropic solution indicates the formation of a nanoemulsion (SNEDDS) percentage of Smix, oil and water. The values were used to prepare pseudoternary phase diagrams. The diagram gives information related to a binary mixture of two components such as water/drug or oil/drug and surfactant/cosurfactant.\textsuperscript{[39]} The corner of this diagram can represent 100% concentration of each phase content. This method drew great attention from scientists in various fields (including pharmaceutical sciences) producing nanoemulsions at room temperature without the use of any organic solvent and heat. Nanoemulsions obtained from spontaneous nanoemulsification processes are not thermodynamically stable, although they might have elevated kinetic energy and long-term colloidal stability.\textsuperscript{[40]}
Preparation of snedds
From the pseudo-ternary phase diagrams, the concentration of oil and surfactant/co-surfactant concentrations is determined and then the formulations can be prepared. The drug and the oil-surfactant mixture are mixed together using a vortex mixer at ambient temperature.\textsuperscript{[41]}

1. Preparation of Liquid SNEDDS
It is an important method for preparation of a self Nanoemulsifying drug delivery system having the oil/surfactant/co-surfactant ratio and surfactant/co-surfactant ratio selected from a pseudoternary phase diagram. The number of series of formulations was prepared by different concentrations of oil, co-surfactant and surfactant. The drug, oil and surfactant were weighed and dissolved and stored at room temperature.\textsuperscript{[42]}

2. Preparation of Solid-SNEDDS
Solid SNEDDS is prepared by using Buchi 190 nozzle-type mini-spray dryers. To prepare solid-SNEDDS, the carriers are suspended in 100 ml of solvent. Hydrophilic carriers are suspended in 100 ml of water and hydrophobic carriers are suspended in 100 ml of ethanol. Some of the examples of solid carriers which are hydrophilic are polyvinyl alcohol (PVA), hydroxypropyl-β-cyclodextrin (HP-β-CD) and sodium carboxymethyl cellulose (Na-CMC) and hydrophobic carriers such as silicon dioxide and magnesium stearate. Silicon dioxide is used mostly as a solid carrier which gives efficient increase in dissolution and oral bioavailability of the drug.\textsuperscript{[42]} To these solutions, liquid SNEDDS are added at room temperature with continuous mixing to obtain good emulsion. The resultant damp mass was passed through sieve no.120 and dried at ambient temperatures.\textsuperscript{[43]}
Fig. 4: Preparation of SNEDDS.

Characterisation of snedds

1. Droplet size
   The droplet size of self-nano emulsifying drug delivery system was determined by photon correlation spectroscopy that analyses the fluctuations in scattering of light due to the Brownian motion of the particle, by using a Malvern Zetasizer (1000HS, UK). The scattered light was monitored at 25°C at a 90° angle. The optimized sample of nanoemulsion was diluted by distilled water, placed in quartz cuvette and they are subjected to droplet size analysis.[43-44]

2. Drug content
   The percent drug content of nanoemulsion system can be analysed using the HPLC.[45]

3. Viscosity
   The Viscosity of self-nano emulsifying drug delivery system is evaluated by Brookfield viscometer for the determination of the consistency of the nanoemulsion formulation.[46]

4. pH
   The pH of the nanoemulsion formulations is measured by pH meter or potentiometer. The electrodes were dipped completely into the semisolid or liquid formulations and the pH was noted.
5. **Surface morphology**
The morphological study gives the information related to the external appearance of the formulation like colour, odour, density, consistency and appearance. In self nanoemulsifying drug delivery system (SNEDDS) globules were observed by the transmission electron microscope (TEM) the sample was visualized and detected.[47]

6. **Percentage transmittance**
Percentage transmittances for the selected SNEDDS were measured immediately after dilution and distilled water is used as a blank to measure absorbance spectrophotometrically using Shimadzu UV-visible spectrophotometer.[48]

7. **Stability studies of SNEDDS via thermodynamic methods**
The SNEDDS were subjected to different stability testing in order to discard the unstable SNEDDS for further studies. The following methods are used to determine the stability such as centrifugation, heating and cooling and freeze-thaw cycles.

8. **Centrifugation study**
The formulations were centrifuged by using the laboratory centrifuge at 5000 rpm for 30 min. The resultant formulations were checked for instability problems, such as creaming or cracking and phase separation. The formulations which are stable are selected for further studies.[48-49]

9. **Heating and Cooling cycle**
Heating-cooling cycles involve six cycles between 4°C and 40°C with storage at each temperature for not less than 24 h. The formulations were evaluated for any phase separation or drug precipitation. Thereafter, the formulations were diluted with distilled water up to 1:25 and they are evaluated for instability issues. The past formulations were selected for further studies.[49-50]

10. **Freeze thaw cycle**
Freeze thawing was done to evaluate the stability of the SNEDDS. It is also known as accelerated aging. The formulations were subjected to 3 thaw cycles, including freezing at -4°C for 24h followed by thawing at 40°C for 24h. Further centrifugation was performed at 3000 rpm for 5min. The formulations were observed for phase separation. The formulations which are stable are selected for further studies.
11. Dispersibility test

The self-emulsification efficiency of oral nano or micro emulsion is determined by using a standard USP XXII dissolution apparatus II. One milliliter of each formulation is added to 500 ml of distilled water at 37±0.5°C. The dissolution paddle which is a stainless steel rotating paddle at 50rpm provides gentle agitation. The in vitro performance of the formulations is determined visually by using the following grading system.

<table>
<thead>
<tr>
<th>Grades</th>
<th>Appearance</th>
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<tbody>
<tr>
<td>Grade A</td>
<td>Rapidly forming nanoemulsion (less than 1min), having a transparent or bluish appearance.</td>
</tr>
<tr>
<td>Grade B</td>
<td>Rapidly forming nanoemulsion, slightly less transparent emulsion, which is having a bluish white appearance.</td>
</tr>
<tr>
<td>Grade C</td>
<td>Fine whitish milky emulsion formed within 2 min</td>
</tr>
<tr>
<td>Grade D</td>
<td>Dull, grayish white emulsion which is having slightly oily appearance that is slow to emulsification process (longer than 2 min).</td>
</tr>
<tr>
<td>Grade E</td>
<td>Formulation, showing either less or minimal emulsification with large oil globules present on the surface.</td>
</tr>
</tbody>
</table>

While formulations which are falling under Grade C could be recommended for SNEDDS as well as SEDDS of formulation.\(^{[51-52]}\)

12. Stability studies

The stability studies are used to determine the quality and purity of the nanoemulsion system. The formulations were determined for its stability by subjecting them to mechanical stress conditions (centrifugation at 2000-4000 rpm) and formulations were stored at different temperatures ranging from 4 ± 1°C to 40 ± 1°C for different time intervals. The effect of the mechanical stress conditions on the stability of the nanoemulsion was observed by determining the breaking of nanoemulsion, percent phase separation or any physical change.\(^{[53]}\)

Novel application of snedds

Supersaturated snedds

Solubility of drugs in lipidic excipients is the main factor that determines the loading dose of drugs in pre-concentrates.\(^{[54]}\) As the lipidic content in SNEDDS is reduced, the solubilizing capability of SNEDDS is declined in-vivo due to dispersion and digestion leading to precipitation of the drugs.\(^{[55-56]}\) Drugs which are more soluble in surfactant or co-surfactant
than lipophilic phase are at a risk of precipitation as the solvent capacity of surfactant and co-
surfactant decreases upon dilution. This is why most of the SNEDDS contain drugs less than
equilibrium solubility (50-90%). Recently researchers concluded that high concentrations of
hydrophilic surfactants also lead to drug precipitation. To overcome this problem
supersaturated SNEDDS (s-SNEDDS) containing hydrophilic precipitation inhibitors have
been introduced successfully.

**Solid snedds**
Conventional liquid SNEDDS (L-SNEDDS) have some restrictions like drug interactions,
drug-excipient interactions and precipitation at lower temperature. Solidification of L-
SNEDDS surpasses these limitations and provides the advantages of improved solubility and
bioavailability, control over the manufacturing process, reproducibility and enhanced
stability.\(^{57-58}\) An alternative for adsorption for solidification is the use of emulsifiers that are
solid or semisolid. The excipient selection for semisolid SNEDDS is based on their melting
points, solubility of drug, HLB values, toxicity, dispersibility and droplet size in different
media.\(^{59-60}\)

**Controlled release solid snedds**
SNEDDS show the pharmacokinetic parameters which are equivalent to oral dosage forms.
SNEDDS produce quick absorption leading to higher peaks \((C_{max})\) with shorter \(T_{max}\) which
leads to high fluctuations in plasma drug concentration. Therefore growing interest is seen in
formulating solid SNEDDS with sustained or controlled release characters.

Various techniques for sustained release SNEDDS include sustained release,
microencapsulation, pellets, gastro-retentive SR tablets, polymer coating, and matrix based
tablets and controlled release osmotic pump tablets.\(^{61-62}\)

**Snedds - As a mucus permeation enhancing strategy**
SNEDDS are better mucus permeating nano carriers. Due to hydrophobic surfaces the
interaction of self-emulsified nano droplets with mucus is low and can cross the mucus layer
without being entrapped. In a research *Friedl et al.* evaluated that the permeation ability of
SNEDDS mainly depend upon the size of generated droplets [less than 50 nm].

**Self double nanoemulsifying drug delivery system**
Drugs like proteins and anticancer drugs are difficult to administer orally in the form of
SNEDDS. Research suggested that thermodynamically stable self-double emulsifying drug delivery systems are also a promising technique for the delivery of hydrophilic activities like peptide and protein drugs.\textsuperscript{[63]} SEEDS consist of hydrophilic surfactant and w/o emulsion which produces w/o/w emulsion upon dilution with water and agitation.

1. Improving the oral delivery of proteins

Oral delivery of peptides is a very challenging task because of high hydrophilicity, poor stability and poor permeability in GI environment. Researchers have developed many strategies for improving the oral bioavailability of proteins. Recently, Shao and coworkers evaluated the ability of the SNEDDS to improve the oral bioavailability of b-lactamase, which is a model protein. Investigators, adsorbed protein on the hydrogenated phospholipids and incorporated into the SNEDDS, and potential of the SNEDDS to improve the caco-2 cell permeability and the oral bioavailability was evaluated. Investigators observed that the peptide-loaded SNEDDS had improved the oral bioavailability. When peptide-loaded SNEDDS are coadministered with the phosphate buffer saline the bioavailability is lower than the protein-loaded SNEDDS diluted with water. The problem with this is leakage of protein from SNEDDS after dilution with aqueous phase. Problem is solved by using an appropriate ion pair for the protein, which increases the lipophilicity of the protein and reduces the leakage.\textsuperscript{[64-66]}

2. Improving the oral delivery of phytochemicals

The majority of the phytochemicals have poor water solubility and poor metabolic stability, which limits their use in the clinic. Researchers have established that SNEDDS can improve the oral bioavailability and therapeutic efficacy of several natural phytochemicals belonging to diverse classes, such as essential oils, alkaloids, carotenoids, triterpenoids and hepatoprotective agents.\textsuperscript{[67]}

Nielsen FS, Petersen KB, Mullertz in 2008 have taken Probucol which is an antihyperlipidemic agent by using Cremophor, Maisine and Sesame oil, they obtained \textit{in vitro} and \textit{in vivo} results predicted that bioavailability of Probucol was increased up to 1.5-3 fold compared with powder.

In case of anti-cancer drugs such as Raloxifene hydrochloride, the uptake of drugs by endocrine organs was assessed by administering the SNEDDS in the alkalized and non-alkalized form to wistar rats. Non-alkalized form showed good uptake by the endocrine
organ than alkalinized form.\textsuperscript{[68]}

\textit{Rao SV, Shao J et al} in 2008 have taken $\beta$ lactamase as a model protein and incorporated into the SNEDDS by using Hydrogenated lecithin, Cremophor EL, Transcutol, Lauroglycol FCC, finally they obtained \textit{in vitro} and \textit{in vivo} results predicted that bioavailability of $\beta$ lactamase was increased up to 2-3 folds when compared with solution.

Sertraline, which is an antidepressant, was formulated as the SNEDDS to improve the solubility and the formulation showed higher drug release and found to be stable over a period of 3 months.\textsuperscript{[69]} A poorly water-soluble beta-blocker talinolol formulated as SNEDDS to enhance bioavailability. The solubility, permeability and drug release is increased than standard drug suspension.\textsuperscript{[70]}

The cardiovascular drug Carvedilol formulated as SNEDDS improved stability over 6 months and enhanced bioavailability. Liquid SNEDDS and also superporous hydrogel which is loaded with carvedilol SNEDDS was prepared which showed an increase in the drug release.\textsuperscript{[71]} Lercanidipine, which is a calcium channel blocker, was formulated as SNEDDS to improve the oral bioavailability and due to its nanosized system the formulation also enhanced the drug absorption.\textsuperscript{[72]} Glibenclamide, formulated as SNEDDS, enhanced the rate of absorption due to nanosized particles and there is no incompatibility between the ingredients.

\textbf{Future perspectives}

Research on SNEDDS technology has gained a lot of importance in the last 10 years and several reports on different formulations of SNEDDS have appeared in the literature. SNEDDS have primarily been explored for enhancement of bioavailability in oral drug delivery, particularly for the low solubility drugs. The pH catalyzed and solution-state degradation of drugs in SNEDDS have been evaluated. The conversion of SNEDDS to a solid state can reduce drug degradation and have been proved and improved. Hence, it is important to identify microenvironment-modulation strategies for improving the stability of pH-sensitive drugs. Many methods have been discovered to convert liquid SNEDDS to a solid dosage form such as tablets and pellets. However, there is a need to identify a suitable highly porous amphiphilic carrier that can convert liquid SNEDDS into a solid powder without significant increase in the volume or bulk density. The applications of SNEDDS in other routes of delivery apart from the oral route can be still explored but still many other
dosage forms have to be developed in the form of SNEDDS which are mainly helpful in the enhancement of the solubility of drugs.

**CONCLUSION**

Self nanoemulsifying formulations have shown tremendous potential in improving the bioavailability of therapeutic agents with limited aqueous solubility. It is a promising approach for BCS class II and IV compounds having poor aqueous solubility. Ease of manufacturing and scale up is one of the most important advantages that make SNEDDS unique when compared to other novel drug delivery systems because it requires very simple and economical manufacturing facilities. The amenability of converting SNEDDS into solid self-nanoemulsifying systems enables development into solid dosage form. Thus, the solid self-nanoemulsifying system can serve as a platform technology for delivering poorly soluble drugs. Although a lot of research is being carried out in this area, other aspects, such as *in vitro/in vivo* correlation, need to be established.

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