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A Review on Self Nano-Emulsifying Drug Delivery System

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ABSTRACT

Self-nanoemulsifying drug delivery systems (SNEDDS) have gained traction as an effective solution for enhancing the solubility of hydrophobic medications. These systems aim to overcome challenges associated with the limited bioavailability of poorly soluble and highly permeable compounds. SNEDDS are composed of isotropic blends of oil, surfactants, solvents, and co-solvents. They have proven to be successful in improving the solubility and bioavailability of drugs that struggle with water solubility. Typically formulated as liquids, various techniques such as extrusion, melting, spray-drying, and freeze-drying have been developed to convert liquid SNEDDS into solid forms. SNEDDS not only demonstrate a notable increase in dissolution rate but also minimize interfacial tension. The continuous advancement of SNEDDS technology is poised to open up innovative applications in drug delivery, offering solutions to challenges associated with the distribution of poorly soluble drugs.

Keywords: Biopharmaceutical classification system, Diffusion, Poor bioavailability, SNEDDS, Surfactant

INTRODUCTION

Oral administration stands out as the most practical and favored route for medication delivery, thanks to its high level of patient compliance. However, a significant drawback arises from the poor water solubility of over 50% of orally administered medications, leading to limited therapeutic effectiveness. Traditional approaches to enhance oral bioavailability, such as salt formation, micronization, solubilization using cosolvents, permeation enhancers, and cyclodextrin complexation, have yielded only partial success and are often specific to particular medication candidates. In response to these challenges, nanotechnology has emerged as a promising avenue in medication delivery research over the past few decades.[1-4]

One notable advancement in this field is the Self Nano-emulsifying Drug Delivery System (SNEDDS), characterized by its isotropic mixture of natural or synthetic oil, surfactants, and co-surfactants. SNEDDS possesses a unique capability to form fine oil-in-water (O/W) nano-emulsions in an aqueous medium with moderate stirring. With globule sizes below 100 nm, SNEDDS disperses effectively in water. Recently, poorly water-soluble drugs have seen improved aqueous solubility through the application of SNEDDS, along with its variants such as Self-Micro Emulsifying Drug Delivery System (SMEDDS) and Self-Emulsifying Drug Delivery System (SEDDS).[5-7]

The formulation of the self-nano-emulsifying medication delivery system for oral consumption involves the use of medium-chain triglyceride oils and nonionic surfactants. SNEDDS proves beneficial in enhancing the rate of drug absorption and maintaining repeatability in drug concentration plasma profiles. Stability of the nanoemulsion is crucial for providing a large interfacial area for drug partitioning between the oil and aqueous phases. To achieve this stability, surfactant and cosurfactant molecules are incorporated into the SNEDDS, resulting in a thermodynamically stable, transparent or translucent, non-ionized dispersion of oil-in-water (o/w) and water-in-oil (w/o) nanoemulsion.[8-10]

The term "Self Nanoemulsifying Drug Delivery System" encompasses various types of stable nanoemulsions, including nanoemulsion, mini-emulsion, ultrafine emulsion, and submicron emulsion. Under moderate agitation, SNEDDS forms a stable oil-in-water nanoemulsion in aqueous media, demonstrating its potential as a versatile and effective approach in overcoming the challenges associated with poor water solubility in oral medication delivery.

Features of SNEDDS[11]

- Able to self-emulsify quickly in GI fluids and with gentle agitation provided by peristaltic movements of GIT, they form fine oil in water emulsion.
- Can efficiently integrate hydrophobic drug or hydrophilic drug inside the mixture of oil surfactant.
- Can be employed for solid as well as liquid dosage forms.
- Require lesser drug dose with respect to conventional dosage forms.

Advantages of SNEDDS[12-13]

- Oral bioavailability enhancement.
- Safe delivery of peptides which are degraded due to enzymatic hydrolysis in GIT.
- Enhanced drug loading capacity with SNEDDS
- Easy in scale up (pilot plant) process.
- No impact on digestion process of lipid.

Disadvantages of SNEDDS [13-15]

- Production costs are high.
- Challenges regarding the validation of different components.
- Problems with drug compatibility.
- Less drug loading due to leakage.
- Traditional dissolution methods do not work.
- High concentration of surface active agent in formulation may cause irritation to GIT.
- Volatile co solvents of SNEDDS migrate into capsule shells, cause precipitation of hydrophobic drugs

Types of Nano-emulsion:
Several Types of Nano emulsions are present which are mentioned in table no. 1

Table no. 1 Classification of Nano-Emulsion[14-15]

Sr. No.	Type	Definition
1.	Water in oil (W/O) Nanoemulsion	In which droplet of water in Continuous Phase oil was dispersed.
2.	Oil in water (O/W) Nanoemulsion	The Oil droplet in Continuous Phase Water was distributed.
3.	Bi-continuous Nanoemulsion	In which surfactant in both the oil and water phase was soluble and droplet was distributed in both the oil and water phase.

Standard Composition of SNEDDS:
Consider the following factors during the development of SNEDDS: entropy changes can lead to increased dispersion, surpassing the energy needed to elevate the dispersion surface. This phenomenon elucidates the conventional emulsion free energy..[16,18]

1. Oil Phase:
SNEDDS, or self-emulsifying drug delivery systems, are blends of oil, surfactants, and cosurfactants that form uniform mixtures. When gently agitated, they produce fine oil-in-water nanoemulsions, suitable for injection into aqueous environments like gastrointestinal fluids. The selection of the appropriate oil is crucial for optimizing drug solubility, influencing emulsion droplet size, and emulsification speed. Effective emulsification requires achieving a small droplet size. To determine drug solubility, High-Performance Liquid Chromatography (HPLC) is employed after medications are mixed with a substance and various oils for an entire night. Evaluating a range of oils aids in identifying the most suitable one, and combinations of oils can be utilized to enhance drug dissolution.

2. Surfactant:
Considering safety as a pivotal factor in surfactant selection for self-emulsifying systems, the formulation may incorporate various compounds exhibiting surfactant properties. However, the options are limited due to the requirement for edibility, favoring emulsifiers of natural origin over synthetic ones for their perceived safety. Non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) are commonly recommended. Achieving stable self-emulsifying drug delivery systems (SEDDs) typically involves utilizing a surfactant concentration ranging from 30% to 60%..(Table No. 2)[19,22]

Table no. 2 Surfactant Group[21]

Sr. No.	Group	Examples
1.	Anionic surfactants	Potassium laurate, sodium lauryl sulphate.
2.	Cationic surfactant	Quaternary ammonium halide.
3.	Ampholytic surfactants	Sulfobetaines.
4.	Nonionic surfactants	Sorbitan esters (Spans), poly – sorbates (Tweens)

3. Co-Surfactant:

In order to achieve a stable interfacial tension, it is often necessary to incorporate co-surfactants alongside a single surfactant. The presence of a co-surfactant is essential as it diminishes the bending stress at the interface, providing flexibility to the interfacial layer. This flexibility is crucial for adopting various curvatures, facilitating the formation of microemulsions and nanoemulsions. Specifically, an HLB cosurfactant in the range of 10-14 is employed in conjunction with surfactants to minimize the oil-water interface, enhance fluidity in the hydrocarbon area of the interfacial film, and promote the spontaneous generation of microemulsions. The careful selection of both cosurfactant and surfactant is pivotal not only for solubilization in microemulsions but also for determining the overall morphology of the microemulsion.[22] (Table No. 3)

Table no. 3 Roles of polymer used in SNEDDS[23,28]

Sr. No.	Category	Examples
1.	Oil Phase	• Fatty acids: Oleic acid, stearic acid, palmitic acid • Fatty acid esters: Glyceryl monooleate, Ascorbyl palmitate, Glyceryl dilaurate, Glyceryl behenate • Propylene glycol esters: Propylene glycol monocaprylate, Propylene glycol dicaprylocaprate • Miscellaneous: Vitamin E, Bees wax, Phospholipids, Stearyl alcohol
2.	Surfactant	• Anionic surfactants: Potassium laurate, sodium lauryl sulphate. • Cationic surfactant: Quaternary ammonium halide. Ampholytic surfactants: Sulfobetaines. • Nonionic surfactants: Sorbitan esters (Spans), poly – sorbates (Tweens)
3.	Co-surfactant	Propylene glycol, polyethylene glycol, polyoxyethylene, Lauroglycol TM, Transcutol

Ideal characteristics of APIs to be incorporated into SNEDDS:

To optimize the oral bioavailability of pharmaceuticals categorized as biopharmaceutical II and IV, self-nano emulsification formulas should meet specific criteria. These include ensuring oil droplet size remains below 100 nm, achieving optical clarity upon dispersion, and having a high HLB value exceeding 12. Table 04 enumerates potential components suitable for incorporation into SNEDDS formulations.[27]

Table no. 4 Suitable drug candidates for SNEDDS[28,34]

Sr. No.	Drug Candidate	BCS Class	Medicated Indications
1.	Valproic acid	I	Anticonvulsants
2.	Calcitriol	II	Vitamin D analogs
3.	Cyclosporin A/I	II	Calcineurin inhibitor
4.	Cyclosporin A/III	II	Calcineurin inhibitor
5.	Saquinavir	IV	Protease inhibitors
6.	Ritonavir	II	Protease inhibitors
7.	Amprenavir	II	Protease inhibitors
8.	Cyclosporine	IV	Immunosuppressive agents
9.	Bexarotene	II	Retinoids
10.	Tipranavir	II	Protease inhibitors

Formulation Techniques for preparation of SNEDDS:
The active medicinal component, excipient, polymers, and emulsifier are all part of the SNEDDS production process. There are several ways to make a self-nanoemulsifying drug delivery system, however they may be essentially split into two categories:

A. High-energy-emulsification.
B. Low-energy-emulsification

High-pressure homogenization (HPH), ultrasonication, and micro-fluidization are integral aspects of the high-energy emulsification process. In contrast, spontaneous emulsification and phase-inversion represent low-energy methods. Reverse Self Nano-emulsifying Drug Delivery Systems are developed by synergizing high-energy emulsification and low-energy emulsification techniques, resulting in the formation of a highly viscous solution.[35,38]

High Energy Emulsification Method:

1. High pressure homogenisation (HPH):
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2. Ultra-sonication:
Reducing drop size through the utilization of the Sonicator-probe method proves to be a more practical approach, as it leverages the energy range provided by sonotrodes. These sonotrodes, acting as Sonicator-probes, can control a piezoelectric quartz stone, regulating the dispersion and constriction of the excited volt. The end tip of the Sonicator makes contact with the liquid medium, inducing a mechanical pulse that captures and confines particles. The formation of captive structures closes vapor cavities in the liquids, resulting in the creation of an emulsion. This technique finds prominent application in laboratories, consistently yielding mixed drops with a canister size of 0.2mm or smaller.

3. Micro-fluidization:
The initial method for incorporating additives in microfluidization involves utilizing a microfluidizer. A disarticulation pump, operating within a pressure range of 500 to 20000 psi, is employed to disrupt the product in the interaction chamber, yielding extremely fine particles in the submicron range. This approach has been consistently applied over many years to achieve the desired range and establish a uniform Nano-emulsion system.[39,42]

Low Energy Emulsification:

1. Phase inversion emulsification method:
Here is a technique used to induce a phase change during emulsification by using a very high temperature pathway.

2. Continuous emulsification:
Emulsification always forms in this system. In which the foundation of consistent and standardised organic resolution is composed of a phase of hydrophilic and miscible surfactants and a grease and lipophilic surfactant infill. Under continuous enticing stirring, the organic point was introduced into the aqueous stage, and string Oil-in-Water was created. As it faded beneath concentrated pressure, the aqueous stage was indifferent.[43,45]

Evaluation Parameters:

Morphology:
Transmission electron microscopy (Cryo-TEM) and small-angle neutron scattering can be used to analyse the SNEDDS morphology (SANS).

Viscosity:
When determining the viscosity of liquid SNEDDS, the Brookfield cone and plate viscometer is typically used. Centipoises (CP), a unit of measure for viscosity that relates to shear rate.

Droplet size and poly dispersity index (PDI):
Using a photon correlation spectroscopy approach, the droplet size and PDI may be determined. To create the preparation, the sample is dissolved at a given concentration in the suitable solvent.

The refractive index (RI):
RI is typically employed to look for transparent formulations. Usually, the refractometer is used to measure the RI. It is also employed to assess the formulation's thermodynamic stability. The minor change in the RI at the various time points of the storage indicates the enduring structure and thermodynamic stability of the SNEDDS.[46]

Zeta potential:
In order to ascertain the particle charge of produced SNEDDS, the Smoluchowski theory is used. The zeta potential indicates the stability of colloidal dispersion. The manufactured formulation is considered stable if the zeta potential is high or greater than 30 mV.

Percentage transmittance:
A UV spectrophotometer is used to measure the system's % transmittance after diluting the formulation at a wavelength of 638 nm and using water as a control. A clear and transparent nature would be indicated by the formulation if the percentage transmittance number is closer to 100%.[47,48]

Self nano-emulsification time:
With the use of dissolving equipment, the effectiveness of self-nano-emulsification is evaluated. Typically, 1 mL of SNEDDS is dissolved in 250 mL of water at a temperature of 370.5°C. A paddle spinning at 50 rpm gives gentle agitation. According to the rate of emulsification and the emulsion's ultimate appearance, SNEDDS are evaluated visually. It is indicated how long the emulsification process took. After emulsification is complete, samples are collected for particle size by photon correlation spectroscopy and further processing by various characterizations.

Thermodynamic stability of emulsion:
The metastable formulation issue is solved using the thermodynamic stability test. For thirty minutes, liquid SNEDDS were centrifuged at 3,500 rpm. For the formulation that showed no evidence of phase separation, the heating and cooling cycle is carried out. With temperatures ranging from 5 to 45 degrees, six cycles will be run over the course of two days. The stable formulation undergoes a freeze-thaw stress test over the course of three cycles over the course of two days at temperatures between -22°C and 25°C. Following this, the formulation that survived or shown stability was chosen as the formulation for subsequent investigations.

Fourier-transform infrared spectroscopy (FTIR) spectral analysis:
FTIR analysis can be used to evaluate drug excipient interactions, polymerization, crosslinking, and drug loading in the formulation. In addition, the molecular fingerprint and the functional groups' modes of attachment are employed to identify them. At low temperatures, molecules are in their ground state, and when they absorb radiant energy, they are stimulated to higher energy levels. IR spectroscopy is used to calculate the energy difference (E) between the excited and ground states of the molecule. The sample can be prepared for FTIR by using an appropriate technique, such as the potassium bromide pellet method or Nujol mulls, and is then scanned in FTIR at a moderate scanning speed between 400 and 400 cm-1.[46,49]

In *vitro* Diffusion study:
For all the formulations created, in vitro diffusion experiments were carried out utilising a diffusion method. The dialysis media was phosphate buffer, pH 6.8. One end of the pretreatment cellulose diffusion tubing (7 cm in length) was attached to the thread before 1 ml of the self-nanoemulsifying formulation and 0.5 ml of the diffusion medium were placed inside of it. Additionally, a thread was used to secure the other end of the tube, which was then allowed to freely rotate in 200 ml of diffusion medium while being constantly stirred at 100 rpm with a magnetic bead on a 37 °C magnetic plate. At different times, 1 ml aliquots were taken out and further diluted. These samples were analyzed quantitatively for drug diffused across the membrane at corresponding time by using UV-visible spectrophotometer.

In *vitro* dissolution profile:
Using a dissolving apparatus Type II in different dissolution media related to the intended route of administration, such as pH 1.2 and pH 6.8 for oral use, the in vitro dissolution profile of the SNEDDS should be assessed. A certain amount of time would be used to collect and analyse the medication that had been dissolved in the dissolving fluid. In comparison to the pure drug, cumulative quantities of drug dissolved versus the periods of the SNEDDS would be shown.

Stability study:
The International Council for Harmonization (ICH) guidelines employed to determine the stability study. The sensitivity towards the moisture and thermal stability tested under different storage conditions for SNEDDS. Usually The ICH storage guidelines for long-term and accelerated stability study are 25°C ± 2°C/ 60% RH ± 5%RH and 40°C ± 2°C/ 75% RH ± 5%RH, respectively.[48, 50]

Market Formulated Product of SNEDDS (refer no. Table no. 5):

Table no. 5 List of Marketed Product

Sr. No.	Brand Name	Drug	Type of Formulation	Application
1.	Convulex/Pharmacia	Valproic acid	Soft gelatin capsules	Anticonvulsant2

2.	Fortovase®	Saquinavir	Soft gelatin capsules	Protease inhibitors2
3.	Rocaltrol/Roche	Calcitriol	Soft gelatin capsules	Vitamin D analogs2
4.	Norvir®	Ritonavir	Soft gelatin capsules	Protease inhibitors3
5.	Agenerase®	Amprenavir	Soft gelatin capsules	Protease inhibitors3
6.	Aptivus®	Tipranavir	Soft gelatin capsules	Protease inhibitors3
7.	Targretin®	Bexarotene	Soft gelatin capsules	Retinoids1

Applications of SNEDDS Drug Delivery Systems:
SNEDDS with pharmaceutically active substances can be employed to create pharmacological formulations. If desired, the combination might be given a particular kind of galena. ampoules, particularly for sterile injection and infusion solutions; Aerosols, which may also contain propellant gas and stabilisers in addition to nanoemulsion, without metering features, and dosing aerosols; hydrophilic and hydrophobic gels, and ointments containing nanoemulsion; solutions, in particular oral liquids, eye drops, and nose drops, which may contain various auxiliary substances; There are creams, lotions, and pastes that include nanoemulsions that are either o/w or w/o.[51, 52]

CONCLUSION

With the use of SNEDDS, the dissolution and absorption rates of weakly water soluble pharmaceuticals might be increased, particularly when absorption rate is constrained by dissolution rate. The methods and excipients used for SNEDDS formulation are low-cost and straightforward. Due to its superior physical stability and simpler manufacture, SNEDDS are becoming more widely used in research. The addition of newer technologies, such as polymer science and biological targeting, to SNEDDS will, from a future viewpoint, significantly advance pharmaceutical research and development.

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