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Emerging Perspective and Future Advancement of Self Nano-Emulsifying Drug Delivery System

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ABSTRACT

The self-nano emulsifying drug delivery system (SNEDDS) is gaining popularity as a means of making hydrophobic medicines more soluble. In order to address problems with limited bioavailability of poorly soluble and highly permeable chemicals, SNEDDS are used. One of the tested techniques for improving solubility and bioavailability of medications that are not well soluble in water is the use of self-nanoemulsifying drug delivery systems (SNEDDS). The SNEDDS are isotropic blends of oil, surfactants, solvents, and co-solvents. The capacity of SNEDDS to create suitable SNEDDS are typically created as liquids, but number of techniques, including extrusion, melting, spray-drying, and freeze-drying, have been developed to turn liquid SNEDDS into solid forms. The enhanced rate of dissolution is clearly demonstrated by SNEDDS, which also minimizes interfacial tension. Due to the extensive development of this technology, SNEDDS will support innovative applications in drug delivery and address issues with the distribution of poorly soluble drugs.

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

INTRODUCTION

Due to the high level of patient compliance, oral administration is the most practical and preferred method for medication delivery. However, due to their poor water solubility, more than 50% of medications administered orally have limited therapeutic effectiveness.[1] To increase oral bioavailability, standard methods such as salt production, micronization and solubilization utilising cosolvents, use of permeation enhancers, and complexation such as cyclodextrin—have been used. However, these methods have only been partially successful and called for a particular medication candidate. Over the past few decades, nanotechnology has greatly increased interest in medication delivery research as a result of this dearth in this processes.[2,4]

The Self Nano-emulsifying Drug Delivery System (SNEDDS) is an isotropic mixture of natural or synthetic oil, surfactants, and co-surfactants that has the rare capacity to create fine oil-in-water (O/W) nano-emulsions with aqueous medium while being moderately stirred. The self-Nano emulsifying drug delivery device has a globule size range of less than 100 nm and disperses in water. Drugs that are poorly water soluble have recently been given a boost in aqueous solubility using the Self-Nano Emulsifying Drug Delivery System (SNEDDS), Self-Micro Emulsifying Drug Delivery System (SMEDDS), and Self-Emulsifying Drug Delivery System (SEDDS). Medium chain tri glyceride oils and nonionic surfactant were used in the formulation of the self-nano-emulsifying medication delivery system for oral consumption. The drug was significant under SNEDDS for improving rate as well as drug absorption and repeatability of drug concentration plasma profile.

The drug was submitted to the dissolving rate limiting absorption.[5,8] To offer a large interfacial area for drug partitioning between the oil and the aqueous phase, it is essential that the SNEDDS be one of the stable nano emulsions. Surfactant and cosurfactant molecules were added to the Self Nanoemulsifying drug delivery system to stabilise the thermodynamically stable, transparent or translucent, non-ionized dispersion of (o/w) and (w/o) nano emulsion. The term "Self Nanoemulsifying Drug Delivery System" is frequently used to refer to nanoemulsion, mini emulsion, ultrafine emulsion, and submicron emulsion (Figure No. 1). Stable o/w nanoemulsion under aqueous media is formed by the Self Nanoemulsifying Drug Delivery System (SNEDDS) o/w nanoemulsion under moderate agitation.[9,10]

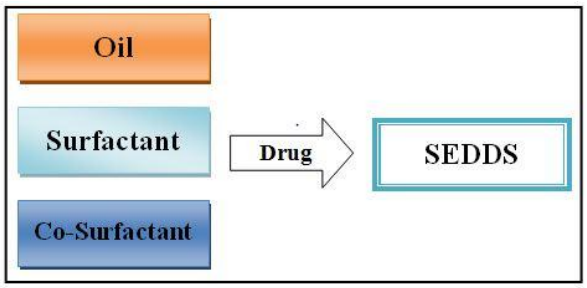

Figure No. 1 Representation of SEDDS, SEDDS is formulated through key ingredient like oil, surfactant and Co-surfactant associated with Drug API

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.

Factor affecting SNEDDS[11]

Unless a drug is very soluble in at least one of the SNEDDS components, ideally in the lipophilic step, it should not be used in SNEDDS at excessively high dosages. The medicines have very little water solubility, and SNEDDS is the most challenging lipid delivery system. The solubility of the medication in the oily phase has a substantial impact on SNEDDS' capacity to maintain the drug in a solubilised form. There may be a probability of precipitation if the surfactant or co-surfactant contributes more to the solubilization of the medication since SNEDDS dilution may cause the surfactant or co-solvent surfactant's potential to decrease.

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-Emulsion14

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:
The following elements are involved in and should be taken into account during the creation of the SNEDDS. Entropy changes would make the dispersion greater than the energy required to raise the dispersion surface, which would explain the conventional emulsion free energy.[16,18]

1. Oil Phase:
When lightly stirred, SNEDDS, which are isotropic combinations of oil, surfactants, and cosurfactants, generate fine oil-in-water nano emulsions that are then injected into aqueous media, such as GI fluids. The oil step should be chosen correctly for the medicine since its qualities regulate the solubility of the drug. This also affects the size of the emulsion droplets and the pace of emulsification. A tiny droplet size is required for effective emulsification. Drug solubility may be determined by HPLC after medications are shaken with a substance and a set amount of different oils for a whole night. So, choosing the best oil may be done by describing a number of oils. Oil combinations may also be used to ensure the drug dissolves as well as possible.

2. Surfactant:
Since safety is a key consideration when choosing a surfactant, the design of self-emulsifying systems may contain a variety of compounds showing surfactant qualities, but the choice is constrained at the same time since very few surfactants are edible. Emulsifiers of natural origin are preferred since they are regarded as safer than surfactants of synthetic origin. The most frequently recommended are non-ionic surfactants with a rather high hydrophilic lipophilic balance (HLB). To formulate stable SEDDs, a surfactant concentration of 30–60% is utilised.(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:
Co-surfactants must be added since steady interfacial tension is seldom achieved when using a single surfactant. The presence of co-surfactant reduces the interface bending stress and gives the interfacial layer the flexibility it needs to adopt the various curvatures required to create microemulsions and nanoemulsions. HLB cosurfactant 10-14 is used in conjunction with surfactants to reduce the oil-water interface, fluidize the interfacial film's hydrocarbon area, and enable the generation of spontaneous microemulsions. The choice of cosurfactant and surfactant is crucial for solubilization in microemulsions, in addition to defining the 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:
Selection criteria for self-nano emulsification formulas Oil droplet size should be smaller than 100 nm, optically clear when dispersed, and HLB value should be larger than 12 in order to enhance the oral bioavailability of pharmaceuticals belonging to biopharmaceutical categories II and IV. Table 04 lists several potential candidates for inclusion in SNEDDS formulation.[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

Higher pressure homogenization (HPH), ultrasonication, and micro-fluidization are all components of the high-energy emulsification process. Spontaneous emulsification and phase-inversion are examples of low-energy methods. Reverse Self Nano-emulsifying Drug Delivery Systems are manufactured by combining both techniques, such as high-energy emulsification and low-energy emulsification, to create a very viscous solution.[35,38]

High Energy Emulsification Method:
1. High pressure homogenisation (HPH):
Homogenization is necessary for the Self Nano-emulsifying drug release system's preparation. This design, which is primarily older than higher-pressurized-homogenizer/location-homogenizer, provides a highly muted particle extent for nano-emulsion (up to 1nm). This hydraulic shear creates very charged emulsion particles by dispersing the blended material into two phases (oil mixture and aqueous phase) quickly with a few minor small cuts at a high pressure (500–5000 psi).

2. Ultra-sonication:
This method of reducing drop size is more practical since the energy range is provided by sonotrodes known as Sonicator-probe. It can restrain a piezoelectric quartz stone that spreads out and tightens the return of a broken excited volt. Sonicator's end tip makes touch with the liquid medium; its container causes a mechanical throb and enrols prisoners. Vapour cavities in liquids are closed up by captive formation. Thus, a straight ultrasonic canister creates an emulsion. This mode is mostly used in laboratories since it consistently produces mix drops with a 0.2mm canister or smaller.

3. Micro-fluidization:
The original addition mechanism for microfluidization makes use of the operation of the aforementioned microfluidizer. A disarticulation pump (with a pressure range of 500 to 20000 psi) was used to break apart the product through the interaction chamber, resulting in very fine particles in the submicron range. This method has been used consistently for a lot of years to obtain preferred range to create an even or homogeneous 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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