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Role of SNEDDS as Novel Approach for Targeted Drug Delivery: A Review

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Abstract

Nanotechnology has become a wide range in pharmaceutical sciences, which has an effect on various drug delivery research from the last 10 years. The developed technology is being explored for the better therapeutic performance of drugs by enhancing the solubility of water-hating drugs (hydrophobic drugs), increasing permeability, regulating drug disposition and biodistribution, and permitting the targeted delivery of drugs. Nanotechnology is broadly categorized into drug nanoparticles or nanosuspension, nanocarriers like lipids, polymeric, and inorganic nanocarriers, as these nanocarriers involve liposomes and microemulsions nanoemulsions, lipid core micelles, solid lipid nanoparticles which are used for the targeted drug delivery systems.2 Based on this technology, the drug components that have poor aqueous solubility, permeability, bioavailability, and instability in physiological medium, the nanoemulsions are selected to enhance the properties. Nanoemulsions are group of heterogeneous with two immiscible liquids as o/w or w/o with droplet size ranges between 20 to 200 nm after the method preparation, before the term nanoemulsions, these are termed as mini-emulsions, micro-emulsions, submicron emulsions, and ultrafine emulsion due to unclear emulsions based on their size of the particles present. Therefore, to overcome the confusion in identifying the actual term, the particles size is within limits or in range, and the main factor is the emulsion, which is indicating transparent, are termed as nanoemulsions and slightly different called microemulsions.

Keywords: Hydrophobic drugs, Nanotechnology, Self-nano Emulsifying Drug Delivery Systems (SNEDDS).

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Introduction

Nanoemulsions have a wide range of advantages for various applications based on the type of delivery system for respective treatment.[1] The novel drug delivery system is the approaches, formulations, technologies, and systems for safely transferring the pharmaceutical compounds to the targeted site in the body and with good therapeutic activity.[2,3] The advantages of nanoemulsions are enlisted:[4,5]

- Long-term colloidal stability
- Ability to solubilize the drugs (hydrophilic and hydrophobic)
- Improved the stability
- Good esthetic application on to the skin
- Increased mucosal and dermal transport process
- Enhanced the oral bioavailability
- Ease of scale-up and manufacture of a formulation

The nanoemulsions will have long term colloidal stability when formulated by the ideal colloidal state. The nanoemulsions are used as drug carriers and have a prolonged shelf-life of products based on the properties.[6] The hydrophilic and hydrophobic drugs in nature will have the ability to solubilize in desired mediums by nanoemulsions depending upon their respective size and emulsions like oil-in-water and water-in-oil. The hydrophobic drugs can improve their solubility by incorporating into oil-in-water nanoemulsions and the hydrophilic drugs are inculcated in water-in-oil nanoemulsions for better solubility of the drugs with the suitable delivery system.[7] The encapsulation of nanoemulsions of therapeutic agents will enhance the stability of respective drugs chemically and enzymatically. For example, cefpodoxime proxetil and 10-methoxy-9-nitro-camptothecin are compounds increasing their shelf-life and stability.[8,9]

As the nanoemulsions are transparent and have less viscosity in nature, due to this property in the formulation there is more patient acceptance, good esthetic appeal, and skin free. Moreover, by adjusting the suitable viscosity in the nanoemulsion preparation, many of the products are in the market like sprays, roll-on-type, nano gels etc.[10]

Drugs like ezetimibe, cefpodoxime proxetil, curcumin, and Ramipril have shown good oral bioavailability in nanoemulsions form.[11] For the preparation of nanoemulsions, there are different methods for making, manufacturing, and scale-up formulation. The various methods are listed below.

Different techniques for the production of Nanoemulsions[12]

1. High energy emulsification methods
   a. Ultrasonication
   b. High-pressure homogenization
2. Low energy emulsification methods
   a. Phase inversion temperature method
   b. Solvent displacement method
   c. Phase inversion composition

Self-nano Emulsifying Drug Delivery Systems (SNEDDS)

SNEDDS are homogenous anhydrous aqueous mixtures that instinctively form oil-in-water (o/w) nanoemulsions by diluting

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Table 1: Biopharmaceutical classification system[18]

Class-I	*Class-II*
High Solubility, High Permeability *Examples:* Diltiazem, Metoprolol *Problems can be minimized by SNEDDS:* dissolution nor absorption rate limiting.	Low Solubility, High Permeability *Examples:* Phenytoin, Mebendazole *Problems can be minimized by SNEDDS:* Dissolution or solubilization rate determination.
Class-III	*Class-IV*
High Solubility, Low Permeability *Examples:* Acyclovir, Neomycin *Problems can be minimized by SNEDDS:* Poor predictability, other mechanisms *in-vivo*.	Low Solubility, Low Permeability *Examples:* Furosemide, Taxol *Problems can be minimized by SNEDDS:* novel alternative approaches to bypass body function.

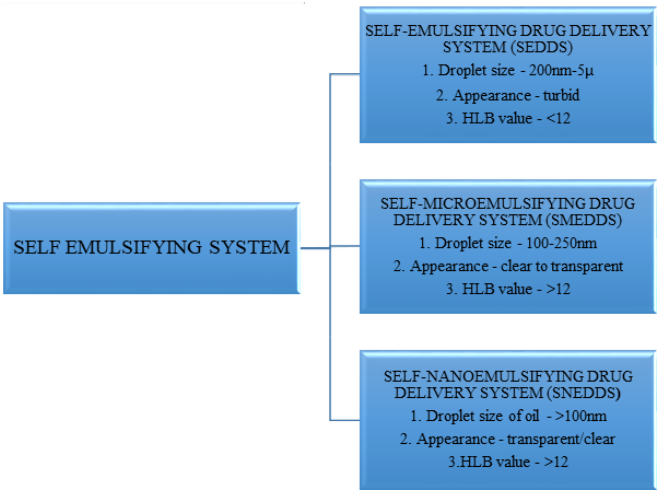

Figure 1: Overview of the self-emulsifying system [13,14]

with distilled water under constant mixing. The prepared self nano emulsifying drug delivery system is having particle size with the range 0 to 200 nm. For the preparation of SNEDDS, it contains various lipids, surfactants/emulsifiers, and co-surfactants/co-emulsifiers in order to solubilize the poorly aqueous soluble drugs, the aqueous solubility of the drug is an important factor for holding the absorption of the drug even after administration and also support for oral bioavailability of a compound.[15] The BCS is an important system for the development of novel compounds. It is a system that identifies the drug components based on its solubility and permeability. Biopharmaceutical classification of the system is categorized by solubility and permeability as these factors will regulate the rate and extent of drug absorption.[16,17]

Advantages of SNEDDS

- It can increase oral bioavailability.
- Safeguards sensitive drug compounds.
- Easy to store, if the compounds are thermodynamic stable.
- Fewer excipients with more drug loading.
- Enhance the physical and chemical stability of the chemical entity for long term storage.
- The formulation can easily be filled into dosage forms such as capsules and improve patient acceptance.[19]

Factors and Components for Preparation of SNEDDS

For the preparation of SNEDDS, few important factors can get the desired formulation and target the specific administration route. The factors are enlisted below:

- The physicochemical nature and the concentrations of oil, surfactant, and co-surfactant should be known.
- The ratios of specific components should be mentioned mainly for oil-to-surfactant.
- At what temperature and pH, the nanoemulsion is taken place should be specific.
- The properties of drug components such as lipophilicity or hydrophilicity, pKa will play a major role in the formulation of a self-nano emulsifying drug delivery system (SNEDDS).[20]

Keeping all these factors in considering an appropriate and transparent SNEDDS can prepare and can target the site by the desired route of administration. For the preparation of SNEDDS, there are mainly three components: oil or lipids, surfactants, and co-surfactants, which are clearly discussed below.

Oil Phase

The oil phase plays a major role in the formulation of SNEDDS, based on its physicochemical properties such as molecular volume, viscosity, and polarity.[21] It solubilizes the lipophilic drug components by protecting it from chemical and enzymatic degradation. The drug distribution in blood and lymph will depend on the Hydrophile-Lipophile balance (HLB) value, chain length, and oil volume.[22] The oily phase has the highest solubilizing capacity for selected drug components and also maximum drug loading can be done in the formulation of SNEDDS. The selected oil should potentially produce the nanoemulsions with the least droplet size of the particles and can formulate the SNEDDS with appropriate and desired characteristics. The oils have different chains of hydrocarbons, such as mono-, di- or triglycerides, and few examples are given in Table 2.

Surfactants

Surfactants or emulsifiers, are safe in oral administration and one of the components used in the formulation of SNEDDS and are amphiphilic. The surfactant selection is based on the HLB value, as natural surfactants have low emulsification capacity and it is one of the limitations in the preparation of SEDS. And the surfactants which are having the highest HLB value be suitable and gives spontaneous nano or microemulsions when it comes in contact with the aqueous state in the gastrointestinal tract. The emulsifier's main role is to increase the bioavailability of SEDS by different mechanisms and of the causes of increased bioavailability is the dissolution of drug components in the prepared formulation.[25] The major properties of surfactants are HLB value, viscosity, cloud point and attraction towards

Table 2: Various oils used in the preparation of SEDDS[23,24]

Class	*Examples*	*Marketed names*
Fixed Oils	Castor oil Soybean oil	-
Fatty acids	Oleic acid Caprylic acid	Crossential O94
Fatty acid esters	Ethyl oleate Isopropyl myristate Isopropyl Palmitate	Crodaml EO
Long-chain & monoglycerides	Glyceryl monooleate Glyceryl mono linoleate	Peceol, Capmul GMO, Maisine 35
Medium chain triglyceride	Triglycerides of capric, caprylic acids Triacetin	Miglyol 810, Labrafac CC, Crodamol GTCC, Captex 300, captex 500
Medium chain, mono, and diglyceride	Mono and diglycerides of capric and caprylic acids.	Capmul MCM, Imwitor 742, Akoline MCM
Propylene glycol fatty acid esters	Propylene glycol mopnocaprylate Propylene monolaurate/dilaurate Propylene dicaprylate & caprate	Capryol 90, Capmul PG 8 Lauroglycol 90, Capmul PG 12, Lauroglycol FCC Miglyol 840, Captex 200
Vitamins	Vitamin E (D-α-tocopgerol)	-

Table 3: Various surfactants used in the preparation of SEDDS[23,24]

Class	*Examples*	*Marketed names*
Polysorbates	Polysorbates 20 sorbitan monooleate and laurate	Tween 80,20 Crillet 4,1
Polyoxyethylene castor oil	Polyoxyethylene 35 castor oil	Cremophor EL Etocas 35 HV
Polyoxyethylene hydrogenated castor oil	Polyoxyethylene 40 hydrogenated castor oil	Cremophor RH 40
Polyoxyethylene stearate	Polyethylene glycol-660-12-hydroxy stearate	Solutol HS 15
Sorbitan esters	Sorbitan monooleate, laurate, stearate	Span 80, Span 20, Span 60

the oily phase and give the minimum droplet size of particles in SNEDDS.[26]

Co-surfactant

The co-surfactant/co-solvent/co-emulsifiers are the solubilizer used in the formulation of SNEDDS and it increases the characteristics in the preparation such as stability, drug loading, self-nano emulsification time, droplet size. And minor limitations are decreasing the solubility of the drug and the volatile nature of the surfactant due to which the evaporation takes place and leads to stability problems.[27] Various co-surfactants used in the formulation of SNEDDS are listed in Table 4.[28-30]

Mechanism of SNEDDS Formation

The self-emulsification is a process that occurs instinctively in the formation of SEDDS. When a change in entropy occurs the surface area of a formed emulsion increases due to greater dispersion of energy.[31] The available free energy will form a surface area between the two different immiscible layers, the immiscible state of emulsions tends to separate out and reduce the interfacial area, which decreases the system's free energy. The stable form system by the aid of an emulsifying agent helps decrease the interfacial tension between two phases. Therefore, in the preparation of SEDDS, the emulsifying agents and co-surfactants are added in the formulation for the reducing the interphasic tension and also lowers the free energy required by the SEDDS when it interacts with an aqueous medium in the

Table 4: Various co-surfactants with their classes[23,24]

Class	*Examples*
Alkane diols and triols	Propylene glycol Glycerol
Glycol Ethers	Diethylene glycol monoethyl ether (Transcutol)
Polyethylene glycols	Polyethylene glycol 400
Short-chain alcohols	Ethanol Benzyl alcohol

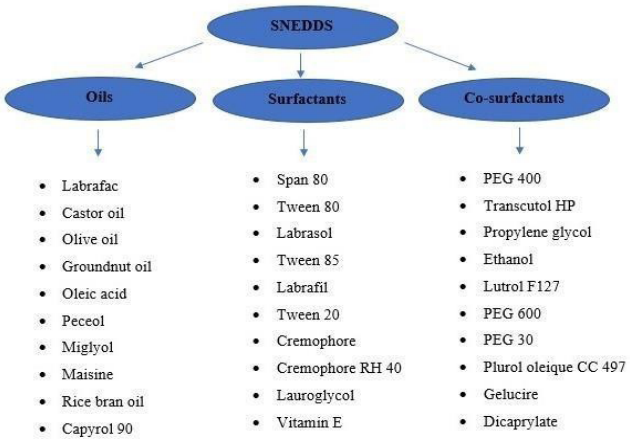

Figure 2: Various solubilizers used in SNEDDS[28-30]

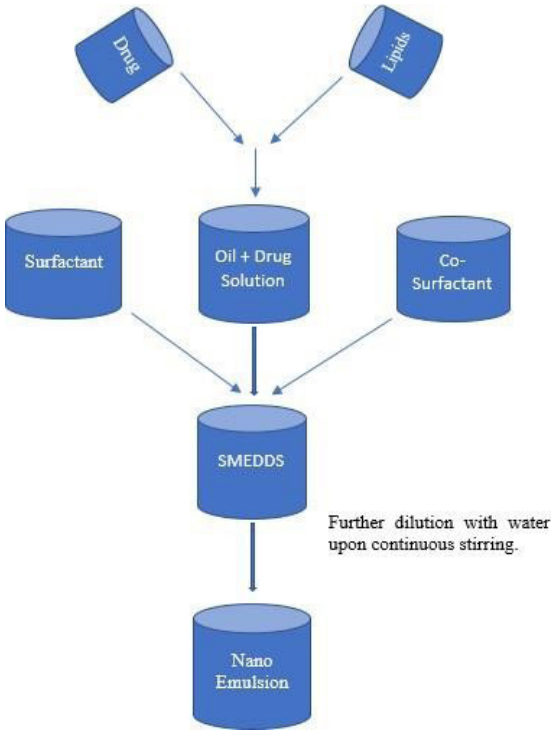

Figure 3: Stepwise procedure for preparation of nanoemulsion[19]

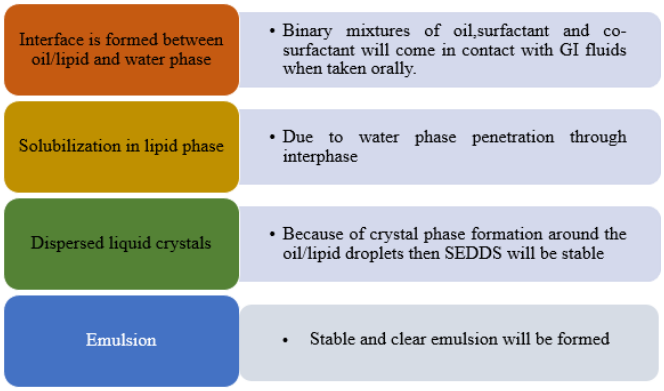

Figure 4: Mechanism of SEDDS formation[31,34]

gastrointestinal tract and then the self-emulsification process occurs with the desired size and site.[32,33]

As per Reiss, the self-emulsification is given in the equation,

$$\Delta G = \sum N \pi r2 \sigma$$

Whereas,

ΔG = Free energy

N = Number of droplets of r and σ

r & σ = radius and interfacial energy

Drug Transport Process of SEDDS

Self-nano emulsification drug delivery systems are prepared for better absorption in the intestinal fluids, the amount of solubilized drug has been increased. Apart from this, absorption of the drug may also be enhanced by using lipid-based excipients in the formulation. SMEDDS/SNEDDS will provide the aqueous insoluble drugs to delivery through oral administration at a specific site with better results. Soon after the drug enters into gastrointestinal tract they go through the following steps i.e.

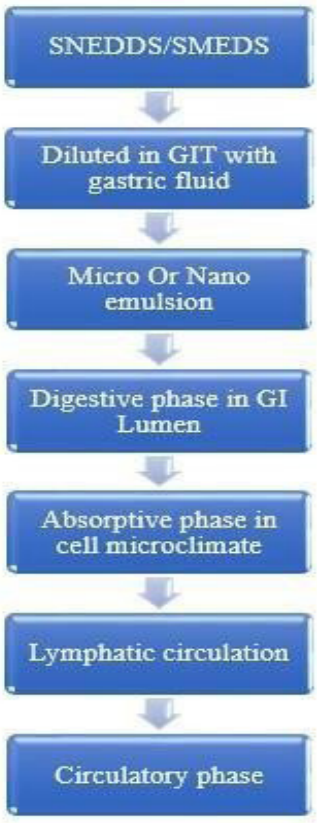

Figure 5: Flow chart of drug transport process[30]

- Digestion
- Absorption
- Circulation

During digestion, SMEDDS/SNEDDS will form into the coarse emulsion, by undergoing enzymatic hydrolysis at oil-water interphase and the emulsion will be set for the next absorption stage. Soon after the formation of heterogeneous micelles, by the interchange of fatty acid in bile, the digestion process will end and soon the drug absorption process will be started. The formed colloids are grabs by the passive diffusion/active transport across the enterocyte membrane. Few of the drug components might get absorbed through the lymphatic circulation and via chylomicrons. In the circulation stage, the drug gets released by chylomicrons, and the body uses excess lipids.[30]

Approaches/Methods for Preparation

Solubility Studies of Solubilizers

The solubility of drug components is checked in various lipids, surfactants, and co-surfactants/co-solvents based on their HLB value. The required amount of drug and 1-mL each oil, surfactant, and co-surfactant is added individually in a clean test tube and then it is followed by mixing through vortex mixer at desired RPM. After vortexing the individual solubilizer, it is undergone for centrifugation at respective RPM for 10 minutes and the obtained supernatant is taken and filtered by a Millipore membrane filter. The collected sample was diluted with a suitable solvent and the drug concentration was observed under UV-visible spectrophotometer.

Initial Screening of Surfactants Emulsifiers

The various emulsifiers were scanned for their emulsification capacity and the appropriate amount of surfactant was added into a fixed ratio of the oil phase. The prepared emulsion was slightly heated at 50°C for uniformity in the drug components and individual mixtures were diluted with distilled water. The prepared emulsion was kept aside for 2 hours, and then % transmittance was checked by UV-Visible spectrophotometer and samples were visually examined for any phase separation, turbidity.[33-34]

Initial Screening of Co-solvent

After the selection and screening of oil and surfactant phases, the next screening is of co-surfactant by various solvents for solubilizing the drug components. Moreover, the samples were diluted with distilled water and obtained its drug concentration by UV-visible spectrophotometer by the respective wavelength of components selected.

Pseudo-ternary Phase Diagram

In this ternary phase diagram, the combination of oil/lipids, surfactant/emulsifiers, and co-surfactant/co-emulsifiers formulation is diluted with distilled water and the ratios are incorporated in the particular software to identify the desired region in which the SNEDDS/SMEDDS are occurring and also used for further optimization of emulsion.[35]

Evaluation Parameters

Self-emulsification Time and Visual Assessment

Different formations were classified based on the RPM of emulsification, transparent and stability for proper and desired emulsion.[36] The visual assessment was done by adding the prepared SNEDDS in 100, 250, and 500 mL of distilled water, 0.1 N HCl and pH 6.8 phosphate buffer in individual beakers by constant stirring on a magnetic stirrer at 1000rpm, then by visual assessment the emulsion is observed for self- nano emulsification efficiency for clear and transparent, turbidity, phase separation and precipitation of drug.[36] The drug precipitation in the prepared emulsion is checked for 24 hours, if the formulation is not showing any kind of precipitation and it is transparent then it shows good emulsification.[37]

Emulsion Droplet Size Analysis

The droplet size is a deciding part in SNEDDS because it controls the rate and extent release of drugs and also the stability of prepared SNEDDS. The droplet size of particles will be determined by dynamic light scattering. After determining the size of the particle, it is further verified by transmission electron microscopy which gives the morphology of particles in emulsion and determines the size distribution of nano and microemulsions.[37,38]

Zeta potential

Zeta seizer is used to knowing the charges of oil droplets in prepared SNEDDS, the charges of oil will also be negative due to the presence of fatty acids,[38] if the SNEDDS shows the higher potential then it will have good stability and long shelf life. If the zeta potential is low, the attractive forces will increase the repulsion between solubilizers, and the emulsion will lead to cracking.[39]

Percentage Transmittance

The formulated SNEDDS was added into different mediums containing 10 mL of water, pH 6.8 phosphate buffer, and 0.1N HCl mixed in cyclomixer for minutes. And the samples are observed for percentage transmittance at respective wavelength.[40]

Drug Content

To know the drug content in the prepared formulation, it was determined by UV-visible spectrophotometer. The desired amount of drug in the formulation was weighed accurately and diluted with suitable solvents. And the diluted formulation is checked under UV-Vis spectrophotometer and the results are incorporated in the equation.[41]

$$\text{Drug loading} = \frac{\text{amount of drug in formulation}}{\text{Initial drug load}} \times 100$$

Transmission Electron Microscopy

The morphology of SNEDDS will be determined by TEM. The diluted L-SNEDDS will be spread on a 200 mesh and the grid is stained with a suitable solvent for 30 second. before analysis, the grid is dried under room temperature and then observed the formulation.[41,42]

Cloud Point Determination

The prepared L-SNEDDS will be diluted with distilled water and deposited in a water bath by gradually rise in temperature. The cloud point will be determined by the appearance of turbidity in the emulsion at a particular temperature and measured by using Nephlo-turbidity meter.[43]

In-vitro dissolution

The dissolution study is performed to know the release of drug content in the optimized formulation. As the study is done by filling the formulation into "0" size hard gelatin capsule shells and the process is carried out by using dissolution test apparatus USP type II which is of paddle stirrer by maintaining the temperature 37± 5°C at 50 RPM of peddle speed. The study will be carried by various mediums such as pH 6.8 phosphate buffer, 0.1N HCl, and water. The buffer medium contains 900mL in the beakers and the samples are collected with the time intervals of 5, 10, 15, 30, 45, 60 minutes and the analyses of the drug concentration is determined by UV-Visible spectrophotometer by the desired wavelength.[44,45]

Conclusion

Self-nano emulsifying drug delivery system (SNEDDS) is one of the novel approaches for targeted drug delivery plays an important role in the pharmaceutical and formulation field. Several formulations have been developed in the past few years, providing the ideas to enhance drug concentration at a specific site and further advancement in this technology and its drawbacks.

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