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REVIEW ARTICLE

Self-Nano Emulsifying Drug Delivery System: A Potential Solution to the Challenges of Oral Delivery of Poorly Water-Soluble Drugs

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ABSTRACT:
Lipid-based drug delivery systems (LBDDS) are the most promising technique to formulate the poorly water soluble drugs. Nanotechnology strongly influences the therapeutic performance of hydrophobic drugs and has become an essential approach in drug delivery research. Self-Nanoemulsifying drug delivery systems (SNEDDS) are a vital strategy that combines benefits of LBDDS and nanotechnology. SNEDDS are now preferred to improve the formulation of drugs with poor aqueous solubility. SNEDDS are isotropic mixtures composed of oils, surfactants, and occasionally cosolvents. The ability of these formulations and methods to produce nanoemulsions or fine oil-in-water (o/w) emulsions after moderate stirring and dilution by water phase along the GI tract. SNEDDS has garnered attention during recent years as it improves oral bioavailability, reduces drug dose, and increases drug protection from unsuitable environment in the gastrointestinal tract. It can solve the problems related to the dissolution and bioavailability of the Biopharmaceutics Classifcation System Class II and IV drugs. This review shortly describes the ambiguity between nanoemulsions and microemulsions, mechanism of self-emulsifications, composition and function of various excipients of SNEDDS. This review discusses characterization of SNEDDS, advantage of SNEEDS over other emulsion, biopharmaceutical aspects, and limitation as well as future views. The SNEDDS is a potential formulation for drug delivery. Owing to its small particle size, large surface area, high encapsulation efficiency, and high drug loading, the SNEDDS can improve the rate and extent of oral absorption by maximizing drug solubility in the intestinal absorption site. Moreover, because of the lipid-based formulation of SNEDDS, it can stimulate and enhance lymphatic transport of drugs to avoid hepatic first-pass metabolism, and thus improve their bioavailability.

KEYWORDS: Oral bioavailability, Solubility, Self-Nano Emulsifying Drug Delivery Systems (SNEDDS), Lipid-based drug delivery systems (LBDDS), Biopharmaceutical aspect.

INTRODUCTION:
Because of its safety patient compliance and ability to self-administer the oral administration route is the recommended method of medicine delivery. Oral delivery has been restricted due to severalbarriers present in the gastrointestinal (GI) tract in addition to being the most convenient form of administration. The solubilization of the medicine inside the GI tract is a necessity for drug absorption as insufficient drug dissolution may eventually lead to partial absorption restricted bio-availability, and significant variability following oral administration[1].

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Various attempts are still being made to raise the oral bioavailability of lipophilic medications to improve their therapeutic efficacy. Various lipid-based formulations have been investigated in recent decades to improve the oral administration of lipophilic medications. In recent years there has been an increase in their integration into self-emulsifying drug delivery systems (SEDDS) with a particular focus on self-nano emulsifying drug delivery systems (SNEDDS). SNEDDS on the other hand, are characterized as isotropic mixtures of natural or synthetic oils solid or liquid surfactants, or alternatively one or more hydrophilic solvents and co-solvents/ surfactants.

When SNEDDS formulations are launched into the gastrointestinal tract's lumen they come into touch with GI fluid and create a fine emulsion (micro/nano) which

is referred to as in situ. The SNEDDS technique was created to deal with the difficulties of formulation and bioavailability. Nano emulsion Mini emulsion ultrafine emulsion and Submicron emulsion are all terms used to describe the Self-Nano Emulsifying Drug Delivery System. This bioavailability- increasing property has been linked to a variety of in-vivo characteristics of lipid formulations including:

Formation of fine dispersions and micelle suspensions to prevent precipitation and recrystallization of the drug component. The ability of certain lipid molecules and their metabolites to induce changes in the gastrointestinal fluid to promote enhanced medication absorption. Inhibition of cellular efflux systems which keep medicines out of circulation. Certain lipid excipients are related to preferential drug absorption into the lymphatic transport system, therefore, decreasing the effect of first-pass drug metabolism it may be conceivable to achieve a uniform distribution.

Self-Emulsifying Drug-Delivery Systems Versus Self-Microemulsifying Drug-Delivery System Versus Self-Self-Nanoemulsifying Drug-Delivery System Formulation:

The major differences between SEDDS, SMEDDS, and SNEDDS are enlisted in Table 1.

Table 1: Major Differences Between Self-Emulsifying Drug-Delivery Systems (Sedds), Self-Microemulsifying Drug-Delivery System (Smedds), and Self-Nanoemulsifying Drug-Delivery System (Snedds) Formulation.

Property	SEDDS	SMEDDS	SNEDDS
Globule size	Greater than 300nm	Less than 250nm	Less than 100nm
Oil phase	40% - 80%	Greater than 20%	Greater than 20%
Surfactants concentration	30% - 40%	40% -80%	40% -80%
HLB value of the surfactant	Less than 12	Greater than 12	Greater than 12
The appearance of the system	Turbid	Optically clear	Optically clear
Classification as per LFCS	Type II	Type IIIB	Type IIIB

HLB: Hydrophilic lipophilic balance; LFCS: lipid formulation classification system

Composition of SNEDDS and their Invovement in Formulation Performance:

Poulton et al.[1] developed the lipid formulation categorization system to make it easier to distinguish between different lipid-based carriers (LFCS). SNEDDSs are classified as class III compositions by the LFCS. The selection of formulation components is critical to the successful formulation of a SNEDDS[2].

API (Active Pharmaceutical Ingredients):

Historically, it was thought that Class II chemicals' very low and varied bioavailability was owing to their poor water solubility. The idea behind using lipid-based DDS like SNEDDS to raise the bioavailability of Class II medications was that co-administration of poorly water-soluble pharmaceuticals with a high-fat meal would improve their bioavailability. BCS class II drugs were selected because SNEDDS is used to increase the solubility of low water-soluble medicines by presenting and maintaining them in a dissolved form. During the transit through the GI tract, the drug is delivered as tiny oil droplets at the molecular level. Drugs that are given at very high doses are not appropriate unless they have exceptionally excellent solubility in at least one of the SEDDS components, particularly the lipophilic phase. The most difficult medications to distribute using SNEDDS are those with a high melting point and poor solubility in water and lipids, often with log P values of approximately 2.

In SNEDDS, The Following Excipients Are Used:

It is very important to select and optimize the quantities of the SNEDDS components. Because the components of SNEDDS and their concentrations will influence the various characteristics of nanoemulsions, such as droplet size, polydispersity index, self-nano emulsification time, and in vitro drug release. In general, the selection of the components based on their ability to solubilize the drug of interest as well as on their ability to form spontaneous emulsions/nano emulsions.

The selection of excipients is very important when it comes to pharmacological acceptability and toxicity concerns. As a result, there is a tight restriction on which excipients should be used. The type, concentration, and oil/surfactant ratio of the oil/surfactant combination, as well as the temperature at which self-emulsification occurs, all have an impact on the oil's capacity to self-emulsify. Once the excipients has been created, excipients that are compatible with the medicine should be evaluated for solubility, compatibility, and stability. The use of a large number of excipients in SNEDDS design is critical. Surfactant, oily phase, and co-surfactant are all components that may be natural, semi-synthetic, or synthetic. The components were chosen to fill the swinging objectives in mind.

- Among the objectives are:
- Achieving maximal drug loading
- Minimizing self-emulsification time and droplet size in the gastric milieu
- Reducing variation in emulsion droplet size
- Preventing or minimizing drug degradation/ metabolism in the physiological milieu.

Oil: Several natural product oils, derived from plant sources and processed to remove impurities or to isolate various fractions of the original product, are available and suitable for use in encapsulated oral formulation products. Not only due to its solubilize property of the

appropriate dosage of the SNEDDS, but also because it is the most significexcipents in the formulation of lipophilic drugs because it has the potential to boost the percentage of lipophilic drugs carried via the expanding the lymphatic system in the intestine dependent on the absorption from the GI tract.

Depending on the molecular nature of the triglyceride, oils can solubilize the required dose of the lipophilic drug and facilitate self-emulsification. Natural edible oils continue to be the most attractive oil components, but they have a very low drug-loading capacity and poor emulsification efficiency.

Long and medium-chain triglyceride (LCT and MCT) oils with variable degrees of saturation have been used to make self- emulsifying compositions. Novel semi-synthetic MCTs, which are classed as amphiphilic compounds with surfactant properties and are progressively and successfully replacing traditional MCT oils in the SNEDDS, are effectively replacing traditional MCT oils. MCT is more soluble and mobile at the lipid/water interface than LCT, allowing for quicker MCT hydrolysis.

Commonly known excipients that used under this category are glyceryl monocaprylocaprate (Capmul® MCM); glyceryl monostearate (Geleol™, Imwitor® 191. Monoglycerides can also be acetylated on their two free hydroxyl groups (Myvacet® 9- 45). Polyoxylglycerides (also named macrogol glycerides by the European Pharmacopoeia) are a well-established class of pharmaceutical excipients for solubility and bioavailability enhancement.

They could be made up of unsaturated long-chain fatty acids. Labrafil® is a type of long-chain fatty acid (LCFA). M1944CS and M1944CS, Labrafil® M2125CS, produced via an alcoholysis/esterification process with saturated medium-chain fatty acids. Gelucire® are acid esters 44/14, produced by an alcoholysis/esterification reaction. Labrafil® M2125CS, made from corn oil and PEG 300), as well as saturated medium-chain fatty acids (SMFA) and PEG 300). Labrafil® M2125CS, generated by an alcoholysis/ esterification reaction with saturated medium-chain fatty acids.

Surfactant:

The surfactant is chosen capable of reducing interfacial tension to a very low value, facilitating the dispersion process and providing a flexible film that can easily deform around the droplets, as well as having the correct lipophilic character to produce the correct curvature at the interfacial region.

Surfactant concentrations in self-emulsifying formulations those were necessary to generate and sustain an emulsion condition in the GI tract typically varied from 30 to 60% by weight. Surfactants in excessive amounts can irritate the GI tract. So the surfactant's safety should be carefully considered in each circumstance. Surfactants with a high HLB and consequent hydrophilicity are required for the process.

Surfactant concentrations in self-emulsifying formulations that were necessary to generate and sustain an emulsion condition in the GI tract typically varied from 30 to 60% by weight. Surfactants in excessive amounts can irritate the GI tract. As a result, the surfactant's safety should be carefully assessed in each circumstance. Surfactants with a high HLB and consequent hydrophilicity are used for the process. A primary concern is safety, a deciding element in the selection of a surfactant. Natural surfactants are preferred over synthetic surfactants because they are safer. The HLB value and safety issue play a role in deciding which surfactant to use in a formulation. Non-ionic surfactants with a high HLB are the most widely used.

The surfactants used in these formulations are known to improve the bioavailability by various mechanisms including:

- Improved drug dissolution,
- Increased intestinal epithelial permeability
- Increased tight junction permeability
- Decreased/inhibited glycol protein drug efflux
- In contrast to ionic surfactants, non-ionic surfactants are nontoxic. Tween 80) and Pluronic F127 are the most often used non-ionic surfactants. The concentration of the surfactant has an inverse effect on the emulsion droplet size. Surfactants in excessive concentrations, on the other hand, infuriate the gastrointestinal mucosa. As a result, safety is a critical consideration when selecting a surfactant molecule. Water-soluble surfactants are the most often used surfactants in self-emulsifying formulations. Cremophor® RH40 and Cremophor® EL that has also been used now a days.

Cosurfactant:

The production of an ideal SNEDDS requires surfactants quite high quantities (usually more than 30% w/w), the surfactant is to reduce the amount of water in the body even if the interfacial tension is minimal negative value. At this point, the interface would grow into finely distributed droplets, causing them to absorb more till their surfactant and surfactant/co-surfactant. The bulk condition has deteriorated to where the interfacial tension is now positive. This is how it works.

Co-surfactant Transient negative interfacial tension is occasionally formed with the application of one surfactant, sometimes requiring the presence of a co-surfactant. The fluid interfacial film is again done by the introduction of a co-surfactant. In the absence of co-surfactant, tremendously rigid film is produced by the surfactant and thus creates microemulsion across only a very thin spectrum of concentration. The inclusion of co-surfactants offers the interfacial layer the elasticity to take up numerous curvatures essential to perform microemulsion within a wide range of compositions. Medium-chain length alcohols (C3–C8), which are extensively active as co-surfactants, have the effect of significantly decreasing the interfacial tension while increasing the fluidity of the contact thereby raising the entropy of the system. The novel cosolvents like Transcutol™ and Glycofurol™ offer various profits over the conventional ones, including greater stability and lower volatility.

Viscosity Enhancers:
The viscosity of the emulsions may be altered by the introduction of additional material such as acetyl alcohol, tragacanth, beeswax, stearic acids, etc.

Polymers:
Polymer matrix (inert) present in 5 to 40 percent w/w, which is not ionizable at physiological pH are achievable to construct matrix. Examples include hydroxyl propyl methylcellulose, ethylcellulose, etc.

Antioxidant Agents:
Lipophilic antioxidants (e.g., α tocopherol, propyl gallate, ascorbic palmitate) stabilize the oily content of SNEDDS formulations.

Mechanism of Self- Emulsification:
Consistent with Reiss, the energy required to enhance the surface area of the dispersion holds less importance as contra to the entropy shift that promotes dispersion. In case of the conventional emulsion formulation, free energy is vital to developing a new interface between the oil and water phases[3].

The net free energy (ΔG) change of the system is calculated using following equation,

$\Delta G = \Sigma N \pi r^2 \sigma$
Where,
N = Number of droplets with radius (r)
σ = Interfacial energy.

As the two phases of the emulsion discrete, the interfacial tension reductions, lowering the system's free energy even supplementary. The primary function of an emulsifier is to reduce interfacial tension. The emulsification process is assisted by the simple entry of water into the many liquid crystals or gel phases designed on the surface of the droplet.

The Effect of SNEDDS' Physicochemical features on in- vivo performance:
The following are observable factors that may stimulate the performance of SNEDDS, but they are not limited.

The Drug's Nature And Dose:
Generally, drug molecules that require higher effective therapeutic concentrations are not considered SNEDDS candidates unless they have extremely good solubility in at least one of the SNEDDS components, rather the lipophilic phase. The most difficult medicines to distribute via SNEDDS are those with low solubility in water and lipids, characteristically with log p values of around 2. The ability of SNEDDS to preserve the drug in a solubilized state is heavily predisposed by the medication's solubility in the oil phase[4].

Surfactant or Co-surfactant Concentration:
If a surfactant or co-surfactant is elaborate, the greater the degree of drug solubilization, the greater the danger of precipitation, since dilution of SNEDDS diminishes the surfactant or co-solvent surfactant's capacity.

Lipid phase polarity status:
One of the key measures determining the efficacy of drug-loaded lipid-based formulations is the type and magnitude of the polarity of the oil/lipid phase. The polarity component is responsible for the types of forces present in the system, as well as the affinity of medication molecules for the oil or water phases. The HLB, the chain length and degree of unsaturation of the fatty acid, and the molecular weight of the micronized medication all encourage the polarity of the lipid phase, which directs drug release from Nanoemulsions. It was exposed that the formulation with the greatest polarity was linked to the fastest medication release rate.

Particle size:
The correct extent of SNEDDS particle size is especially important in the case of per oral administration, as it may have a direct stimulus not only on in-vitro measured parameters (e.g., stability and release kinetics) but also on in- vivo performance. Smaller droplet size, as measured in vitro, has a positive influence on the bioavailability of the medication incorporated into SNEDDS. As a result, it is reasonable to conclude that particle size distribution has a significant influence on the oral bioavailability of medication included in SNEDDS.

Zeta Potential:
High zeta potential (>30mV) directs significant electrostatic repulsive forces, ruling out the possibility of electrostatic attraction. The presence of flocculation suggests the formation of stable SNEDDS. SNEDDS are supplied as a pre-concentrate formulation that induces nano-dispersion, the in-vitro long-term stability of the resultant nano-emulsion is less important. Nonetheless, the charge of the particles formed may influence the medication incorporated into SNEDDS' oral bioavailability. There have been reports of charge-dependent interactions with human intestine cells in the context of absorption enhancement. As a result, it can be contingent that particle size and charge may affect not only particle stability and release kinetics but also the amount of absorption of the inserted medication.

Preparation of SNEDDS:
The preparation needs the addition of medicine to the combination of oil, surfactant, and cosurfactant. The drug is dissolved in any one of the excipients and the remaining excipients are added to the drug solution. Then, the solution should be suitably mixed and inspected for indications of turbidity. After equilibration at ambient temperature for 48hours, the solution should be heated for the formation of clear solution. The formulation should be kept in capsules of suitable size.

Optimization of SNEDDS Formulations:
After recognizing probable components of SNEDDS, optimization experiments are carried out to achieve the optimal quantities of oily phases, surfactants, and cosolvents that could yield spontaneous Nanoemulsion. Ternary phase diagrams are commonly employed to discover the emulsification area for given components. In ternary diagrams, the ratio of one component fluctuates while the concentrations of the other two are constant. The emulsification area is recognized visually or by measuring the particle size of the emulsion/ nanoemulsion arising after aqueous dispersion. All the SNEDDS compositions from the emulsification region generate spontaneous Nanoemulsions, with globule diameters less than 200 nm after water dispersion[5].

In addition to a ternary phase diagram, SNEDDS optimization may also be skillful using other statistical experimental designs, such as Box–Behnken design, Central composite design, Simplex lattice design, Full-factorial design, and D-optimal design. A feature of these statistical experimental designs is that they may cut expenses in terms of time, resources, and development efforts.

The formulation by design approach has recently concealed the conventional end product testing method in the pharmaceutical business. An Approach to Quality through Design QbD is a unique technique for creating high-quality pharmaceutical items. Application of QbD ideas in the production system allows a thorough product and process knowledge to develop a trustworthy product that assures both safety and effectiveness. QbD acts as a bridge between industry and the drug regulatory bodies to develop a comprehensive and productive, scientific, risk-oriented approach to pharmaceutical product design of SNEDDS.

Characterization of SNEDDS:
It is often vital to assess the final SNEDDS for numerous criteria. The basic methods and processes that have been implemented for SNEDDS characterization include followings[6-7].

Thermodynamic Stability Studies:
This study is grave for product performance because drug precipitation in the excipient matrix could have a negative impact. Poor formulation physical stability can prime to excipient phase separation, which can distress bioavailability and medicinal efficacy.

Heating and Cooling Cycle:
Six cycles will be tested between 40°C and 4°C in the refrigerator, with storage at each temperature for at least 48 hours. The compositions that persist stably at these temperatures are then centrifuge tested.

Centrifugation:
After passing through the heating-cooling cycle, the formulas are centrifuged for 30 minutes at 3500 pm. The freeze-thaw stress test is achieved on formulations that do not display any phase separation.

Freeze-Thaw Stress Cycle: Those formulations that pass this test show respectable stability with no phase separation, cracking, or creaming after three freeze-thaw cycles between -21°C and 25°C and storage at each temperature for not less than three months. The formulations that pass this test are afterward subjected to a dispersibility test to govern their ability to self-emulsify.

Dispersibility Test:
The dispersibility test of SNEDDS is performed to evaluate its capacity to disperse into emulsion and classify the size of the globules that outcome. It is done out with the help of a standard USP dissolving device 2 (paddle type). At 37 °C, one ml of each formulation is added to 500 ml of water and the paddle revolved at 50 rpm. The SNEDDS formulation generates nanoemulsion quickly (within 1 minute) when titrated with water; a clear or blue tint displays production of Nanoemulsion.

Particle Size and Morphology:
Scanning electron microscopy (SEM) and transmission electron microscopy (TEM) may be used to investigate the morphology of Nanoemulsion droplets. Cryo-SEM and cryo- TEM have recently been developed to inspect the true morphological information of Nanoparticles. According to the research works, smaller particle size expands the oral bioavailability of a drug encapsulated in SNEDDS. The kinetic stability of the resulting emulsion is confirmed by the small mean droplet size, which proposes a broad interfacial surface for drug absorption.

Drug content:
The drug is pulled out from pre-weighed SNEDDS by dissolving it in a suitable solvent. A suitable analytical method is used to regulate the drug content in the solvent extract.

Zeta Potential:
The colloidal stability might be determined using the zeta potential. The electrophoretic mobility of the droplets is used to compute it. The presence of a high zeta potential (40 mV) specifies the presence of repulsive electrostatic forces, which decreases the prospect of particle aggregation.

Viscosity Testing:
The SNEDDS system is available in both soft and hard copies. It should have satisfactory flow characteristics for manufacturing gelatin capsules. Although excessively viscous SNEDDSs are seldom included in capsules owing to flowability limits, low-viscosity formulations face leaking issues. Spinning viscometers, digital equipment attached to either a cup and bob or a coaxial measurement device, were used to estimate the rheological parameters of the composition.

Percent Transmittance and Refractive Index (R.I.):
To control the transparency of a formulation, the refractive index and percent transmittance is calculated. The refractive index of the formulation is resolute using a refractometer and a drop of solution on a slide, which is then compared to water. Using a UV spectrophotometer and clean water as a blank, the % transmittance of the formulation is measured at a certain wavelength.

Diluted Resistant Emulsions:
When dilution with different dissolving mediums, emulsions should not show any phase separations or drug precipitation even after 12 hours of storage; such formulations are measured dilution resistant.

Measurement of Cloud Points: The cloud point is defined as the temperature at which the emulsion clarity develops cloudy because of the dehydration of the polyethylene oxide moiety of nonionic surfactants. After diluting the preconcentrate 100 times with distilled water and placing it in a water bath with an advanced rise in temperature, the cloud point could be established. In addition, spectrophotometric experiments are carried out to govern the sample's transmittance percent. The increase in transmittance may be exploited to keep track of the situation.The nanoparticle droplet size is usually connected to the self-emulsification rate and the eventual transmittance percent.

In-vitro Diffusion Experiment:
The purpose of this research is to examine the release behavior of a formulation utilizing the dialysis method, which typically uses phosphate buffer (pH 6.8) as the dialyzing medium. One end of the dialysis membrane is threaded, and 1 ml of the SNEDDS formulation is put into the membrane, along with 0.5 ml of dialyzing fluid. The other end of the membrane is tied with thread and spun at 100 rpm in dialyzing fluid using a magnetic stirrer or dissolving device. At various periods, samples are taken and assessed.

Technique for In-Vitro Dissolution:
The in-vitro dissolution experiments are accomplished using USP type 2 dissolving equipment with 500 ml of simulated gastric juice containing 0.5 percent w/v of SLS at 50 rpm at a temperature of 37 °C to quantify drug release from the oil phase into the aqueous phase. At various periods, aliquots of samples are taken and evaluated using a UV spectrophotometer or other relevant procedures.

SNEDDS Influence on solubility:
The medication molecule can only partition into the enterocyte and eventually cross it if it is provided in its dissolved state. The provision of the whole dosage in a solution is the principal method by which lipid-based formulations expand pharmaceutical solubilization. The digestion of lipid-based formulations containing SNEDDS aids in the absorption of nutrients. The solubilized phase is almost certainly produced from the intra-luminal processing to which lipids are exposed before absorption, rather than directly from the given lipid-based formulation.

Endogenous biliary-derived solubilizing components such as bile salts and biliary lipids (cholesterol and phospholipids) are secreted more often when lipid and lipid- digestion products are present in the duodenum. Bile enhances the solubility of lipid digestion products in the aqueous intestinal lumen. The nonpolar hydrocarbon chain forms the core, whereas the polar

group of micellesprotrudes into the aqueous phase. The formation of the aqueous mixed micellar phase suggestively increases the small intestine's solubilization ability.

When a poorly water-soluble medication is united with lipids found in food or the formulation, the drug is distributed among various colloidal forms. This method inhibits drug precipitation and increases the effective aqueous solubility of the weakly water-soluble co-administered molecule. Furthermore, the usage of SNEDDS makes a broad interfacial region that allows the integrated lipophilic drug to be partitioned between oil and the GI fluid[8].

The Influence of SNEDDS on Permeability:

Increased transcellular permeability was anticipated as a potential cause for improved oral bioavailability when SNEDDS was used. One of the proposed mechanisms for this existence is the interaction of SNEDDS components with the enterocyte membrane, which results in increased fluidity and, as a result, increased passive permeability. SNEDDS components affect membrane fluidity, which might change the shape of membrane-bound transporters and increase the inhibition of membrane-bound efflux transporters. As a significance, a reduced efflux causes an increase in drug permeability. They may be two separated systems. It's also probable that the drug's enhanced permeability as a result of SNEDDS use is because of a combination of increased passive transcellular transport and efflux inhibition[9].

SNEDDS Improvement of Oral Absorption:

Many animal investigations were directed to determine the oral bioavailability of hydrophobic medicines synthesized in SNEDDS. During medication advance, pharmacokinetics studies are crucial for determining oral bioavailability in humans. There are hundreds of them.Pharmacokinetics studies with SNEDDS formulations represent increase d bioavailability in animals such as rats, dogs, and rabbits, as well as in humans. Tables 2 and 3 afford examples of bioavailability increases in SNEDDS formulations and select commercial formulations respectively[10].

Advantages of Self-Nano Emulsifying Drug-Delivery system over other Emulsions

SNEDDS offers the following advantages[11]:

- Irritating responses of the active moieties due to prolonged exposure could be overcome after employing SNEDDS preparations that promote the transportation of active molecules from the tiny globules through the GI tract.
- After dispersion in the aqueous phase, these preparations develop tiny globules having a tremendous interfacial region that normally promote partitioning of the medication from oil to the aqueous phase.
- SNEDDSs are beneficial as compared to typical emulsions when they are associated with their stability due to the incorporation of less energy as well as the production process, which usually do not employ some difficult steps.
- The medications, which exhibit less solubility in the aqueous medium, also show rate limited absorption that usually depends upon the dissolution rate. In this context, SNEDDS could be absorbed effectively with a subsequent constant plasma time profile.
- SNEDDS consists of distinct emulsifying agents, for example, various Spans, Tween 80, Cremophor EL, Pluronics, which are observed for exhibiting inhibitory effect with regard to efflux transporters that assist in enhancement of the bioavailability of the active molecules that are usually act as a substrate usually to the efflux pumps.
- The drug molecules that have a tendency to be destroyed via the chemical substance, as well as enzymes in the GI tract, could be shielded by the SNEDDS, while the active agents are being distributed to the body by incorporating them in the oil globules.
- Microemulsion preconcentrate is beneficial over other typical microemulsion formulations to distribute active moieties by means of liquid packed in the capsules prepared using the soft gelatin.

Biopharmaceutical aspects for formulation design:

SNEDDS have a concealed to increase oral bioavailability through multi-concerted techniques. SNEDDS give medications in a minute droplet size and regular dispersion and increase the dissolution and permeability. Furthermore, since pharmaceuticals may be loaded in the inner phase and provided via lymphatic bypass sharing, SNEDDS guard drugs from hydrolysis by enzymes in the GI tract and decrease the pre-systemic clearance in the GI mucosa and hepatic first-pass metabolism. The following features should be considered for correct formulation of SNEDDS[12-16]:

Since a very high concentration of surfactants is commonly utilized in the SNEDDS formulation, toxicity of the surfactant being used should be thoughtful. In reality, a compromise must be established between the toxicity and self- emulsification capabilities of the surfactant that is selected for usage in preparation.

- An inclusive exposition of pre- selecting excipients for their fatty acid makeup melt properties, HLB or emulsification qualities, possible encouragement on enterocytes-based drug transport and temperament, and overall digestibility.
- Conducting broadcasts with the preselected

excipients for drug solubility, compatibility, stability and dissolution/dispersion properties to establish suitable systems for future investigations.
- Identifying the formulation technique fit for the dosage form planned as well as confirming the in vivo efficacy of the selected formulation system in apprehension animal models.
- Regulating the compositions per individual physicochemical features and absorption processes of a drug.
- Proper acquaintance with the spontaneous emulsification process, physicochemical and biological characteristics of the components hired for the formation of SNEDDS are important for the formulation of SNEDDS.

Future Perspective, Limitation and Conclusion:

Pharmaceutical chemists have advanced many formulations to increase the BA of hydrophobic medicines. SNEDDS is a promising approach with several benefits, including remarkable stability, improved appropriateness of hydrolysis-sensitive medicines, high drug loading capacity, and ease of manufacture. The SNEDDS improves the solubility of BCS Class II medications as well as the permeability of BCS Class III and IV therapies, as well as reducing inter/intra-patient dosage variability. SNEDDS advances medicine absorption in a variety of ways.

Previously, SNEDDS was used to challenge problems with pharmaceutical solubility and bioavailability. The opportunity of SNEDDS, on the other hand, is much broader than dissolution and solubility. To address challenges with simple SNEDDS and advance new adaptations for various applications, they have grown into supersaturated, solid, regulated, and targeted SNEDDS in recent years.

Solid SNEDDS were intended for ease of handling, manufacture, and stability, whereas supersaturated SNEDDS was shaped to improve drug loading capacity. Regulated SNEDDS eliminated plasma drug fluctuations, and targeted SNEDDS avoided drug detrimental effects on normal tissues. Targeted SNEDDS diminished adverse effects of drugs on normal tissues, while regulated SNEDDS avoided plasma drug fluctuations. Another issue is how to select a careful and optimum ratio of components in SNEDDS. One possible way out is to replace traditional hit and trial method by HLB-response surface technique. This technique can minimize cost and cutshort the number of formulations needed to identify the optimum composition. Despite the prior achievements, there are still areas where SNEDDS desires to improve to become a future drug delivery carrier. Even though various appreciated and predictive in-vitro tests have been developed to better understand SNEDDS, we still lack suitable in-vivo data since small animals have less stomach fluid than humans, which may not be adequate for proper self-emulsification. The composition of the SNEDDS should be established quite carefully. Since a relatively high concentration of surfactants is commonly utilized in the formulation may have unfavorable side effects such as stomach pain during treatment. As a result, a formulation with stronger self-emulsifying properties at lower concentrations is essential. Currently, pharmacological products developed as SNEDDS such as Cyclosporine A, Ritonavir,Tretinoin as etc, are freely accessible on the market. As roughly 40% of novel drug compounds are hydrophobic, it predicts that further drug products for the pharmaceutical industry will be formed as SNEDDS in the coming years.

Table 2: Application of SNEDDS in formulating low solubility and permeability drugs

Drug	Components	In Vivo Observation	Ref. No
Vitamin E	Palmoil,Tween®80,Span®80	3-fold higher oralbio-availability from SNEDDS	17
Curcumin	Ethyl oleate, Tween 80, PEG 600	The characterized SNEDDS shows a better bioavailability compared to curcumin suspension	18
Cyclosporin	Cornoilglycerides,Cremophor®RH40,PG DL-α-tocopherol and ethanol	AUC_{0-t} andCmax increased 1.18 and 1.17 fold, respectively from SNEDDS.	19
Tocotrienols	Tocomin, Soybean oil Tween® 80Labrasol®	2 to 3 fold higher oral bio-availability from SNEDDS.	20
Diacereine	Maisine oil, Tween 80, Cremophor EL, Transcutol HP	Improvement in dissolution, portal absorption and lymphatic delivery of diacereine	21
Simvastatin	Labrafil®,Tween®80, Transcutol HP	1.55 and 1.5 increased in Cmax and AUC_{0-t}, respectively from SNEDDS	22
Vitamin K	Vitamin K, Labrasol®, Transcutol HP	Enhancement in vitamin K relative bio-availability From SNEDDS	23
Tamoxifen	Olive oil, Tween 80, PEG 400	Enhancement of bioavailability compare to pure Drug	24
Bortezomib	Glycerol monooleate, Tween 80,Trancutol-P	Characterized SNEDDS shows improved intestinal absorption	25
TicagrelorB	Capmul MCM, Cremophor EL, Transcutol HP	The optimized formulation shows high solubility, increases therapeutic activity with better bioavailability	26
Etodolac	Phosal 53 MCT, Labrasol, PEG 400	Enhancement of dissolution characteristics	27
Huperzine	Castor oil, Cremophor RH40, Propylene glycol	The optimized formulation shows enhanced lymphatic absorption & improves the bioavailability	28

Table 3: Application of SNEDDS in formulating low solubility and permeability drugs

Drug Name	Trade Name	Company	Dosage Form
Tretinoin	Vesanoid®	Roche	Soft Gelatin capsules
Tipranavir	Aptivus®	Boehringer Ingelheim	Soft Gelatin capsules
Cyclosporine A	Gengraf®	Abbott Laboratories	Hard Gelatin capsules
	Sandimmune®	Novartis	Soft Gelatin capsules
Isotretinoin	Accutane®	Roche	Soft Gelatin capsules
Paricalcitrol	Zemplar®	Abbott Laboratories	Soft Gelatin capsules
Ibuprofen	Solufen®	Sanof-Aventis	Hard Gelatin capsule
Tolterodine tartrate	Detrol LA®	Pharmacia	Extended release Hard Gelatin capsule
Lopinavir and Ritonavir	Kaletra®	Abbott Laboratories	Soft Gelatin capsules

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