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Review Article

Self Nano-Emulsifying Drug Delivery System: an updated Review

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ABSTRACT

Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have emerged as a promising strategy to overcome the limitations associated with the poor aqueous solubility and low oral bio-availability of hydrophobic drugs. SNEDDS are isotropic mixtures of oil, surfactant, co-surfactant, and drug that spontaneously form fine oil-in-water nanoemulsions upon mild agitation in gastrointestinal fluids.

The resulting nanoscale droplets (<100 nm) provide a large surface area for drug dissolution, enhancing absorption and improving pharmacokinetic profiles. SNEDDS formulations are thermodynamically and kinetically stable, and can be optimized using pseudo-ternary phase diagrams. Both liquid and solid SNEDDS are prepared using techniques such as high-pressure homogenization, microfluidization, sonication, and phase inversion. These systems are particularly effective for Biopharmaceutical Classification System (BCS) Class II and IV drugs and have demonstrated enhanced bioavailability in various in vivo studies.

Key evaluation parameters include droplet size, zeta potential, thermodynamic stability, dispersibility, viscosity, and drug content. SNEDDS also provide protection against enzymatic degradation and enable targeted and sustained drug release. Despite formulation challenges such as surfactant-induced irritation and long-term stability concerns, SNEDDS represent a versatile and efficient approach for oral and alternative drug delivery routes, with broad applications across pharmaceuticals, nutraceuticals, and cosmetics.

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INTRODUCTION

Self Nano-emulsifying drug delivery systems (SNEDDS) are anhydrous homogenous liquid mixtures consisting of oil, surfactant, drug, and co-surfactant or a solubilizer, which spontaneously form oil-in-water Nanoemulsion of approximately 200nm or less in size upon dilution with water under gentle stirring (1). Recent years Self Nano-emulsifying Drug Delivery System (SNEDDS), self micro-emulsifying Drug Delivery System (SMEDDS), and self-emulsifying drug delivery systems (SEDDS) are used to improve the aqueous solubility of poorly water-soluble drugs (2). 'SEDDS' is a broad term, typically producing emulsions with a droplet size ranging from a few nanometers to several microns. "Self-microemulsifying drug delivery systems" (SMEDDS) indicate formulations forming transparent microemulsions with oil droplets ranging between 100 and 250 nm (3). SNEDDS shows good bioavailability of the highly lipophilic, poorly water-soluble drug by various mechanisms but also can improve oral bioavailability of hydrophobic drugs by several mechanisms. The formulation of self Nano-emulsifying Drug Delivery System was formulated using medium-chain triglycerides oils and non-ionic surfactant, which is important for oral ingestion (4). The drug was subjected to the dissolution rate-limiting absorption, and the drugs under SNEDDS are important for enhancement of rate as well as drug absorption and reproducibility of plasma profile of drug concentration (5). The SNEDDS is one of the stable Nanoemulsions, important to provide a large interfacial area for partitioning of drug between oil and aqueous phase, having a better rate of drug dissolution and increasing bioavailability of drug formulation (6). The Self Nano emulsifying Drug Delivery System is thermodynamically stable. It is a transparent or translucent non-ionized dispersion of (o/w) and (w/o) Nanoemulsion stabilized by the addition of surfactant and co-surfactant molecule. The SNEEDS is also known as Nanoemulsion, mini emulsion, ultrafine emulsion, submicron emulsion (7). SNEEDS offer a more efficient and reliable way to deliver poorly soluble drugs compare to conventional drug delivery systems, addressing many challenges associated with solubility, ability and bioavailability.

Mechanism of self –emulsification

According to Reiss, the energy needed to increase the surface area of the dispersion bear less importance as compared to the entropy change that favors dispersion (8). In case with the conventional emulsion formulation, the free energy is required to create a new surface between the oil and water phases. The net free energy (ΔG) change of the system is calculated by following equation,

$$\Delta G = \sum N \pi r^2 \sigma$$

Where, N= Number of droplets with radius (r) and σ = Interfacial energy.

The reduction in the interfacial tension occurs as the two phases of the emulsion separate out which further minimize the free energy of the system(s), The main function of emulsifier is to reduce the interfacial tension and thus protection of coalescence, The readily penetration of water into several liquid crystals or gel phases formed on the surface of the droplet facilitates

emulsification process (9-11, 42).Co-solvents assist in maintaining a uniform drug solution. They can reduce the viscosity of the formulation, aiding in dispersion. Co-solvents ensure that the drug does not precipitate. Their use depends on the drug's properties and the formulation goals. Too much co-solvent can affect stability, so it must be balanced. Co- solvents also influence the overall bioavailability of the drug. In SNEDDS, co-solvents add flexibility to the formulation (40).

Types of SNEDDS

Water in oil (W/O) Nanoemulsion (12)

Water-oil (W/O) nanoemulsions are a type of colloidal system in which tiny droplets of water are dispersed within a continuous oil phase. These nanoemulsions are typically stabilized by surfactants or emulsifiers to prevent the droplets from coalescing. The droplet size in nanoemulsions is typically in the range of 10–200 nanometers, making them optically transparent or translucent and highly stable compared to conventional emulsions.

Oil in water (O/W) Nanoemulsion (12)

Oil-in-water (O/W) nanoemulsions are systems in which tiny droplets of oil are dispersed within a continuous water phase. Like water-in-oil (W/O) nanoemulsions, O/W nanoemulsions have droplet sizes typically in the range of 10–200 nanometers, giving them high stability, transparency, and desirable physicochemical properties.

Bicontinuous Nanoemulsion (13)

Bicontinuous nanoemulsions are a unique type of nanoemulsion where both the oil and water phases form interconnected, continuous networks rather than having one dispersed in the other. This structure is stabilized by surfactants and co-surfactants, which create a dynamic balance at the oil-water interface, allowing the coexistence of two continuous phases. The droplet size in bicontinuous nanoemulsions typically falls in the nanoscale range (10–200 nm).

Advantages of SNEDDS

By forming a stable Nanoemulsion in the gastrointestinal tract, SNEDDS increase the surface area for absorption, promoting faster and more consistent drug release (14). Self Nano-emulsifying Drug Delivery Systems (SNEDDS) enhance the solubility and bioavailability of poorly water-soluble drugs, leading to improved therapeutic outcomes (15). They also protect drugs from enzymatic degradation, ensuring better stability and reduced variability in plasma levels (16). SNEEDS play a crucial role in achieving ultra-low interfacial tension and generating large O/W interfacial areas, which are essential for enhancing drug solubility and bioavailability (17). SNEEDS are

formulated in various forms such as liquids, sprays, foams, creams, ointments and gels. They are widely used as Nanoemulsions in the pharmaceutical industry and serve as effective drug delivery systems for oral, topical and parenteral application (18). In SNEEDS oils and their main components are essential and have numerous application in medicine, food, beverages, preservation, cosmetics as well as in the fragrance and pharmaceutical industries (19). It is used as Ayurvedic system and unnani system (20). The SNEEDS having site specific as well as targeted drug delivery systems (21).

Disadvantages of SNEDDS (22, 23)

Despite their benefits, Self Nano-emulsifying Drug Delivery Systems (SNEDDS) have certain limitations. Formulating SNEDDS requires careful selection of compatible oils, surfactants, and co-surfactants, which can be complex and costly. SNEDDS may also cause gastrointestinal irritation due to high surfactant concentrations. Additionally, SNEDDS can have stability issues over time, such as phase separation or precipitation of the drug, potentially reducing effectiveness.

Appropriate Drug Candidate for SNEEDS (24)

The Self Nano-emulsifying Drug Delivery System (SNEDDS) is a novel approach for enhancing the oral bioavailability of poorly water-soluble drugs. In the Biopharmaceutical Classification System (BCS), drugs are classified into four classes. Class II and Class IV drugs have lower water solubility compared to Class I and Class III drugs. Therefore, SNEDDS is particularly beneficial for Class II and Class IV drugs as it can increase water solubility and improve oral bioavailability. Additionally, SNEDDS is important for preventing the problem of enzymatic degradation associated with Class I and Class III drugs, thus offering improved solubility and bioavailability.

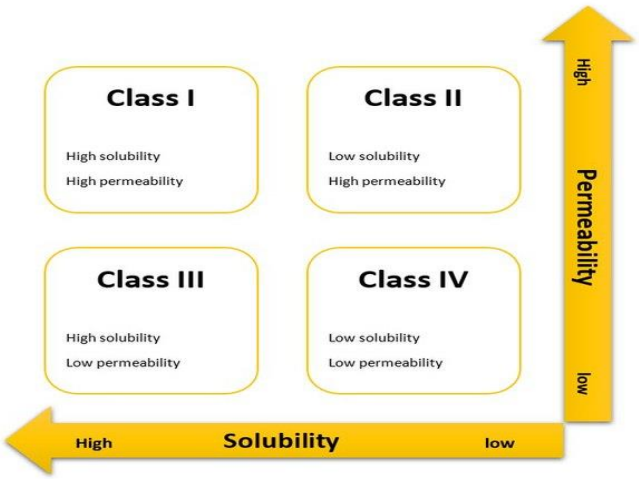

Figure 1: Biopharmaceutical Classification system (BCS)

Comparison of SNEDDS and SMEDDS

SMEDDS	SNEDDS	Reference
It is Self-Micro emulsifying drug delivery system	It is Self -Nano emulsifying drug delivery system	**25**
It is turbid in nature	It is transparent in nature	**26**
Large amount of energy is required for preparation as compare to Nanoemulsion	Less energy required for preparation	**27**
Droplet size is 100-300nm	Droplet size is less than 100nm	**28**
It is thermodynamically stable	It is thermodynamically and kinetically stable	**29**
It is optimized by ternary phase diagram	**It is optimized by Pseudoternary phase diagram**	**30**

Figure 2: Image of Emulsion, Micro-emulsion and Nanoemulsion

Components of SNEDDS

1. Oil: The oil component in SNEDDS is crucial for dissolving lipophilic drugs, improving their solubility. It serves as the carrier that interacts with other components to form a Nanoemulsion. Oils in SNEDDS can be medium-chain triglycerides (MCTs) or long-chain triglycerides (31-33). These oils help in achieving the desired droplet size in the Nanoemulsion. MCTs are often preferred for their rapid digestion and absorption. Oils can vary based on their compatibility with the drug being formulated. They act as a key element in controlling drug release rates. Oils also enhance the drug's overall bioavailability when ingested orally. The right oil selection can improve formulation stability. Overall, oils are foundational in the SNEDDS formulation process (34, 35). Nowadays, MCT has been replaced by novel semi-synthetic MCTs, which play an important role in enhancing the water solubility of poorly soluble drugs. Oil phases are modified using vegetable oils, digestible or non-digestible oils, and fats, such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, and hydrogenated oil, to improve solubility (36).

2. Surfactant: Surfactants reduce the interfacial tension between the oil and water phases. They help in forming stable Nano-sized droplets when mixed with water. Polysorbates (such as Tween) and PEG derivatives are common surfactants in SNEDDS. The surfactant concentration is critical to maintain stability without causing toxicity. Surfactants also aid in achieving the transparency of SNEDDS formulations. They support drug dispersion and prevent precipitation. An ideal surfactant should be safe, effective, and non-irritating. The surfactant's role extends to enhancing absorption in the gastrointestinal tract. High concentrations may cause irritation, so balance is essential. Surfactants are thus central to SNEDDS stability and functionality (37, 38).

Classification of Surfactant molecules (39)

Surfactant molecule is mainly classified into 4 types:

Anionic surfactant: The hydrophilic group carries negative charge is known as Anionic surfactant.

Example- potassium laurate, SLS

Cationic surfactant: The hydrophilic group carries positive charge is known as cationic surfactant.

Example- Quaternary ammonium halide

Ampholytic surfactant: The surfactant unit consists of both charges positive as well as negative charge.

Example -sulfobetaines

Non-ionic surfactant: The hydrophilic group carries no charge but derives its

water solubility because it can contain strong polar functional groups such as hydroxyl or polyoxyethylene. Example - sorbitan esters (spans) Polysorbates

3. Co-surfactant: Co-surfactants work alongside surfactants to further stabilize the emulsion. They help in lowering the amount of surfactant needed. Common co-surfactants include ethanol and propylene glycol. Co- surfactants assist in achieving the desired Nano-droplet size. They enhance the solubility of poorly soluble drugs. Co-surfactants contribute to the thermodynamic stability of SNEDDS. They play a role in preventing phase separation over time. The choice of co-surfactant affects the drug release rate. Co-surfactants make the formulation more versatile. In SNEDDS, co-surfactants ensure both efficacy and stability. Co-surfactant example like ethanol, methanol, pentanol, glycol, propylene (40).

4. Drug: The drug is the active component that SNEDDS aims to deliver. Typically, the drug is poorly water-soluble, requiring enhancement in bioavailability. The SNEDDS formulation helps improve the drug's oral absorption. By dissolving in the oil phase, the drug is ready for Nano-emulsification. The drug's compatibility with SNEDDS components is essential. SNEDDS provide a large surface area for drug absorption. The drug must remain stable in the Nanoemulsion form. Effective SNEDDS can deliver a consistent drug dose. The SNEDDS system reduces drug degradation in the body. Overall, the drug is central to the therapeutic purpose of SNEDDS.

5. Co-solvent (optional): Co-solvents can improve the drug's solubility within the SNEDDS formulation. They are not always necessary but can be helpful in certain cases. Ethanol and glycerine are common co-solvents used in SNEDDS. Co-solvents assist in maintaining a uniform drug solution. They can reduce the viscosity of the formulation, aiding in dispersion. Co-solvents ensure that the drug does not precipitate. Their use depends on the drug's properties and the formulation goals. Too much co-solvent can affect stability, so it must be balanced. Co- solvents also influence the overall bioavailability of the drug. In SNEDDS, co-solvents add flexibility to the formulation (40).

Table 1: Example of Surfactants, co-surfactants, co-solvents, lipids or oils (41, 42)

Excipient Name (Commercial Name)	Examples of commercial products
Surfactants/co surfactants	
Polysorbate 20 (Tween 20)	Targretin soft gelatin capsule
Polysorbate 80 (Tween 80)	Gengraf hard gelatin capsule
Sorbitan monooleate (Span 80)	Gengraf hard gelatin capsule
Polyoxyl-35-castor oil (Cremophor EL)	Gengraf hard gelatin capsule, Ritonavir soft gelatin capsule
Polyoxyl-40-hydrogenated castor oil (Cremophor RH40)	Neoral soft gelatin capsule, Ritonavir oral solution
Polyoxyethylated glycerides (Labrafil M 2125Cs)	Sandimmune soft gelatin capsules
Polyoxyethylated oleic glycerides (Labrafil M 1944Cs)	Sandimmune oral solution
D-α-Tocopheryl polyethylene glycol 1000 succinate (TPGS)	Agenerase soft gelatin capsule, Agenerase oral solution
Co-solvents	
Ethanol	Neoral soft gelatin capsule, Neoral oral solution, Gengraf hard gelatin capsule, Sandimmune soft gelatin capsule, Sandimmune oral solution
Glycerin	Neoral soft gelatin capsule, Sandimmune soft gelatin capsule
Propylene glycol	Neoral soft gelatin capsule, Neoral oral solution, Lamprene soft gelatin capsule, Agenerase soft gelatin capsule, Agenerase oral solution, Gengraf hard gelatin capsule
Polyethylene glycol	Targretin soft gelatin capsule, Gengraf hard gelatin capsule, Agenerase soft gelatin capsule, Agenerase oral solution
Lipid ingredients	
Corn oil mono-, di-, tri-glyceride	Neoral soft gelatin capsule, Neoral oral solution
DL-α-Tocopherol	Neoral oral solution, Fortovase soft gelatin capsule
Fractionated triglyceride of coconut oil (medium-chain triglyceride)	Rocaltrol soft gelatin capsule, Hectorol soft gelatin capsule
Fractionated triglyceride of palm seed oil (medium chain triglyceride)	Rocaltrol oral solution
Mixture of mono- and di-glycerides of caprylic/capric acid	Avodart soft gelatin capsule
Medium chain mono- and di-glycerides	Fortovase soft gelatin capsule
Corn oil	Sandimmune soft gelatin capsule, Depakene capsule
Olive oil	Sandimmune oral solution

Oleic acid	Ritonavir soft gelatin capsule, Norvir soft gelatin capsule
Sesame oil	Marinol soft gelatin capsule
Hydrogenated soybean oil	Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
Hydrogenated vegetable oils	Accutane soft gelatin capsule, Vesanoid soft gelatin capsule
Soybean oil	Accutane soft gelatin capsule
Peanut oil	Prometrium soft gelatin capsule
Beeswax	Vesanoid soft gelatin capsule

Preparation of SNEDDS (43) SNEDDS is prepared in 2 ways

1) Solid SNEDDS Preparation

Solid Self Nano-emulsifying Drug Delivery Systems (SNEDDS) are meticulously crafted to enhance the solubility and bioavailability of hydrophobic drugs. The preparation involves transforming liquid SNEDDS into a solid form by adsorbing onto carriers such as silica, microcrystalline cellulose, or malt dextrin. Advanced techniques like freeze-drying or spray-drying solidify the formulation while maintaining the integrity of the Nanoemulsion. This approach not only improves drug stability but also enhances handling and processing during manufacturing, making it suitable for tablet or capsule forms.

2) Liquid SNEDDS Preparation

Liquid SNEDDS are formulated through the strategic blending of the active pharmaceutical ingredient with oils, surfactants, and co-surfactants to spontaneously form a Nanoemulsion upon dilution with gastrointestinal fluids. This sophisticated process creates a pre-concentrate that, under mild agitation, self-emulsifies into fine droplets. Encapsulation in gelatine capsules often follows, ensuring rapid release and enhanced absorption. This method is favoured for its simplicity and efficacy in enhancing drug solubility and bioavailability in liquid formulations.

Method of Preparation of SNEDDS

The high-energy approach

The high-energy approach for Nanoemulsion formation relies on a precisely selected mixture composition, including surfactants, co-surfactants, co-solvents, and functional compounds. To achieve the Nanoemulsion, significant energy is applied to the mixture, enabling the ingredients to interact and form stable Nano-sized droplets. The emulsification process involves intense mechanical processing, such as high-pressure homogenization, ultra sonication, or micro

fluidization, to break down and disperse particles at the nano scale. This method provides fine control over droplet size and uniformity, making it highly effective for enhancing the solubility and bioavailability of poorly soluble drugs (44).

High Pressure Homogenizer

The high-pressure homogenizer is a key instrument for producing Nanoemulsions with exceptionally fine droplets. In this method, an oil-in-water surfactant mixture is subjected to very high pressure and pumped through a resistive valve. The intense shear stress within the device breaks down the mixture into ultra -fine emulsion droplets. Droplet size reduction is explained by the combination of turbulence and cavitation; as the high-velocity mixture flows through the homogenizer, turbulent eddies of a similar size to the mean droplet diameter are generated, fragmenting the droplets. Simultaneously, the pressure drop across the valve induces cavitation, creating additional eddies that further disrupt the droplets. By decreasing the gap size, pressure increases, leading to an enhanced cavitation effect and even finer emulsification. Emulsion droplets as small as 100 nm can be achieved with adequate surfactant coverage at the oil-water interface, which stabilizes the Nanoemulsion and prevents droplet coalescence (44).

Micro fluidization

Micro fluidization is a key technology for detecting and preparing Nanoemulsions, utilizing a device called a "Micro fluidizer." This device operates with a high-pressure positive displacement pump (500-3000 PSI), which forces the mixture through an interaction chamber composed of micro channels. As the mixture flows through these micro channels, it reaches an impingement area where high shear forces break down the particles into a fine submicron range, forming a Nanoemulsion. The oil and aqueous phase mixture initially forms a coarse emulsion, which, when processed in the Micro fluidizer, becomes a stable, homogeneous, and transparent Nanoemulsion. This approach ensures a controlled, fine particle size distribution, enhancing the Nanoemulsion's stability and effectiveness (45).

The sonication method

The sonication method is essential for reducing droplet size in conventional emulsions and accurately determining droplet size in Nanoemulsions. Through ultrasonic waves, this technique applies high-frequency energy to disrupt larger droplets, breaking them into smaller particles. This method is particularly effective for small batches, as the intense

energy helps achieve Nano-sized droplets with improved uniformity. Sonication is ideal for research and formulation development, offering precise control over droplet size in Nanoemulsions, which enhances stability and bioavailability (45).

The phase inversion method

The phase inversion method is crucial for preparing micro emulsions and Nanoemulsions, utilizing temperature-based responses to induce emulsion formation. In this process, physical and physicochemical changes, such as variations in particle size and in vivo/in vitro drug release rates, occur as temperature shifts. By adjusting the system's temperature, non-ionic surfactants facilitate a spontaneous transition in emulsion type. At lower--temperatures, oil-in-water (o/w) Nanoemulsion forms, while at higher temperatures, water-in-oil (w/o) Nanoemulsion develops. This method provides precise control over droplet structure and stability, enhancing the efficiency and effectiveness of Nanoemulsion formulations for drug delivery (46).

The pseudo ternary phase diagram

The pseudo ternary phase diagram is essential for determining the optimal composition of a Self Nano- emulsifying Drug Delivery System (SNEDDS). This diagram represents the ratios of oil, surfactant, co-surfactant (Smix), and water in a triangular plot, helping to identify the zones where Nanoemulsions form. Constructed through phase titration or phase inversion methods, the procedure involves preparing mixtures with various ratios of surfactant to co-surfactant, such as 1:1, 2:1, or 3:1. These solutions are then vortexes for five minutes to achieve an isotropic mixture and are visually evaluated for clarity. A turbid appearance indicates a coarse emulsion, while a clear, isotropic mixture suggests successful Nanoemulsion formation. By recording the percentage compositions of oil, Smix, and water, a pseudo ternary phase diagram can be constructed, with each corner representing 100% concentration of one phase component. This diagram provides critical insights into the compatibility and stability of various binary mixtures (e.g., surfactant/co-surfactant, oil/water) and helps optimize formulations by pinpointing the precise emulsion-forming region for SNEDDS development (47).

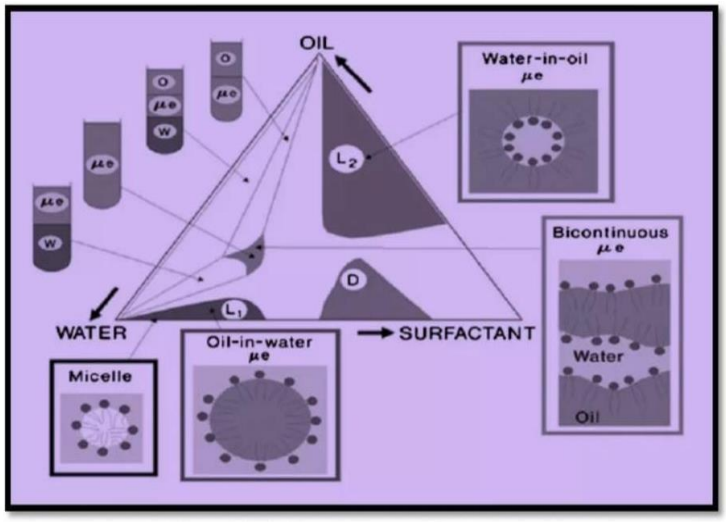

Figure 3: Pseudo ternary phase diagram

Evaluation of Self Nano-emulsifying Drug Delivery System (SNEDDS)

Thermodynamic stability of emulsion

The thermodynamic stability of lipid-based formulations plays a critical role in their efficacy, as instability may lead to drug precipitation within the excipient matrix, compromising the overall performance. Furthermore, poor thermodynamic stability in formulations can induce phase separation among excipients, impacting not only the functional attributes of the formulation but also its aesthetic appeal. To ensure optimal drug delivery and enhance the therapeutic potential of SNEDDS, maintaining a robust stability profile is paramount (48).

Centrifugation Study

The formulations underwent centrifugation at 5000 rpm for 30 minutes using a laboratory centrifuge. Following centrifugation, each sample was meticulously examined for any signs of instability, including phase separation, creaming, or cracking. Only formulations demonstrating robust stability were selected for subsequent studies. This step is essential to ensure that the formulations maintain their structural integrity under stress conditions, as any signs of instability could compromise efficacy. Through this screening, we identified stable formulations with the potential to deliver consistent therapeutic results (48).

Heating and Cooling Cycle

The formulations were subjected to three heating and cooling cycles, fluctuating between 4°C and 40°C, with a minimum storage time of 24 hours at each temperature. Post-cycling, these formulations were meticulously evaluated for thermodynamic instability markers,

such as phase separation and precipitation. Only formulations that successfully passed this rigorous test were advanced for further analysis. This stability check is crucial for identifying robust formulations that can withstand temperature variations, enhancing their viability for real-world applications (49).

Freeze-Thaw Cycle

The freeze-thaw cycle was utilized to assess the stability of SNEDDS under extreme temperature shifts. Formulations underwent three cycles, each involving freezing at -4°C for 24 hours, followed by thawing at 40°C for another 24 hours. After each cycle, centrifugation was performed at 3000 rpm for 5 minutes, after which the formulations were closely monitored for any phase separation. This process enabled the optimization of Smix concentrations, ensuring the final formulations exhibit strong resilience against thermal stress and maintain consistent performance (49).

Droplet Size

The droplet size of the Self Nano-emulsifying Drug Delivery System (SNEDDS) was measured using photon correlation spectroscopy, which analyzes fluctuations in light scattering caused by the Brownian motion of particles, with a Zetasizer 1000HS (Malvern Instruments, UK). Light scattering was observed at 25°C at a 90° angle. For accuracy, the optimized Nanoemulsion sample was diluted with distilled water, placed in a quartz cuvette, and subjected to droplet size analysis, ensuring precise characterization of particle dimensions (50).

Viscosity

The viscosity, a key rheological property of SNEDDS, was assessed using a Brookfield Viscometer to determine the consistency of the Nanoemulsion formulation. This evaluation is essential, as viscosity can directly influence the emulsification performance and stability of the formulation. By obtaining accurate viscosity measurements, we can better understand the flow behaviour and adaptability of the Nanoemulsion under various conditions. Such insights are critical for optimizing the SNEDDS for efficient drug delivery and ensuring a stable formulation suitable for long-term use (51).

Stability Study

The stability study is essential for assessing the quality, purity, and durability of the Nanoemulsion system under various stress conditions. Stability was evaluated by exposing multiple Nanoemulsion formulations to mechanical stress, including centrifugation at 2000-4000 rpm, and storing them at controlled temperatures ranging from 4 ± 1 °C to 40 ± 1 °C across varied time intervals. To

ensure a comprehensive evaluation, each formulation was also analyzed for potential chemical degradation under these conditions. The impact of mechanical stress on the physicochemical stability of the Nanoemulsion was further assessed by observing parameters like percent phase separation, emulsion breakdown, or any physical changes. Formulations that demonstrated no significant alterations after 60 minutes of centrifugation at 2000 rpm were considered robust and suitable for extended applications (52).

Drug Content

Assessing the percent drug content and purity of the Nanoemulsion system is critical for maintaining both the quality and therapeutic consistency of the formulation. In this evaluation, twenty tablets were individually weighed to establish an accurate average weight. Afterward, the tablets were finely ground to achieve a uniform sample consistency. An exact portion of the powdered sample was weighed, dissolved in an appropriate solvent, and serially diluted to prepare it for High-Performance Liquid Chromatography (HPLC) analysis, as per the dissolution testing protocol. This approach ensures precise quantification of the active drug content in the Nano-emulsion system, providing essential insights into its stability and performance for therapeutic applications (53).

Dispersibility Test

The efficacy of self-emulsification for oral nano or microemulsions is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation is carefully added to 500 ml of water maintained at a temperature of 37 ± 0.5°C. Gentle agitation is provided by a stainless steel paddle rotating at 50 rpm. The emulsification performance of each formulation is evaluated visually based on the following grading criteria:

Grade A: Rapidly forms (in less than 1 minute) a Nanoemulsion, characterized by a clear or bluish appearance. Grade B: Forms quickly with a slightly less transparent, bluish-white look.

Grade C: Produces a fine whitish milky emulsion that appears within 2 minutes. Grade D: Displays a dull, greyish-white emulsion with a slightly oily texture.

Grade E: Shows minimal emulsification, with large oil droplets evident on the surface.

Formulations classified as Grade A and Grade B are expected to maintain their Nanoemulsion state when dispersed in the gastrointestinal tract (GIT), which is crucial for optimal drug release (54).

Morphological Study

The morphological study is essential for providing insights into the external

characteristics of the formulation, including color, odor, consistency, and density. In the case of Self Nano-emulsifying drug delivery systems (SNEDDS), the globules were examined using a transmission electron microscope (TEM) to gain a deeper understanding of their structure and uniformity. This high-resolution imaging allows for the visualization and characterization of the globule size and shape, which are critical factors influencing the performance of the Nano- emulsion. Additionally, these observations can help in assessing the overall quality of the formulation (55).

pH Measurements

The pH of the Nanoemulsion formulations was determined using a calibrated pH meter or potentiometer. Electrodes were fully immersed in the semi-solid or liquid formulations to obtain accurate pH readings. Maintaining the appropriate pH is crucial, as it can significantly impact the stability and bioavailability of the formulation. Regular monitoring ensures that the formulations remain within the desired pH range for optimal efficacy (56).

Percent Transmittance

The percent transmittance of the Nanoemulsion formulation (SNEDDS) was quantified using a UV-Visible double beam or single beam spectrophotometer, with distilled water serving as the blank at a wavelength of 560 nm. This measurement provides valuable information about the clarity and stability of the formulation, as higher transmittance typically indicates better quality and uniformity. Analyzing percent transmittance is integral to ensuring that the Nanoemulsion formulations are suitable for their intended applications, particularly in enhancing drug delivery (57).

Improvement of oral absorption by SNEDDS (58)

Many studies carried out in animals for the assessment of the oral bioavailability of hydrophobic drugs formulated in SNEDDS. Pharmacokinetics studies play a major role in predicting the oral bioavailability in humans during drug development. There are hundreds of published articles on pharmacokinetics studies with SNEDDS formulations, reporting enhanced bioavailability in animals such as rats, dogs, or rabbits, as well as in human. Examples of bioavailability enhancement of SNEDDS formulations and some of the marketed formulations are mentioned in Table 2 and 3, respectively.

Table 2: pharmacokinetics data reporting enhanced bio-availability from SNEDDS in human subjects.

Drug	Component	In vivo observation
Vitamin 3	Palm oil, Tween® 80, Span® 80	3-fold higher oral bio-availability from SNEDDS
Cyclosporine	Corn oil glycerides, Cremophor® RH40, PG DL-a-tocopherol and ethanol	AUC_{0-t}, and Cmax increased 1.18 and 1.17 fold, respectively from SNEDDS
Tocotrinols	Tocomin, Soybean oil, Tween® 80, Labrasol®	2 to 3 fold higher oral bio-availability from SNEDDS
Saquinavir (Fortovase®)	Medium-chain mono- and di-glycerides	Increased oral bio-availability up to 331% from fortovase® compared to invirase®.
Simvastatin	Labrafil®, Tween® 80, Transcutol HP	1.55 and 1.5 increased in Cmax and AUC respectively from $SNEDDS_{0-t}$
Vitamin K	Vitamin K, Labrasol®, Transcutol HP	Enhanced in vitamin K relative bio-availability from SNEDDS

Table 3: Non-exhaustive list of marketed SNEDDS for oral administration

Drug name	Trade name	Company	Dosage forms
Tretinoin	Vesanoid®	Roche	Soft gelatin capsules (10mg)
Tipranavir	Aptivus®	Bochringer ingelheim	Soft gelatin capsules (250mg)
Cyclosporine A	Gengraf®	Abbott	Hard gelatin capsules (25,100mg)
	Sandimmune®	Novartis	Soft gelatin capsules (25,50,100mg)
Isotretinoin	Accutane®	Roche	Soft gelatin capsules (10,20,40mg)
Lopinavir and ritonavir	Kaletra®	Abbott	Soft gelatin capsules lopinavir 133.33mg and Ritonavir 33.3mg

Application

Enhancing Water Solubility of Poorly Soluble Drugs (59)

The Self Nano-emulsifying Drug Delivery System (SNEDDS) plays a pivotal role in augmenting the water solubility of poorly soluble drugs, significantly enhancing their oral bioavailability. This innovative approach to drug delivery has been successfully employed across various domains, including cosmetics, transdermal systems, cancer therapeutics, and vaccine administration. The application of Nanoemulsions in drug delivery also extends to enhancing the oral

bioavailability of poorly soluble drugs, as well as facilitating ocular, otic, intranasal, parenteral, and pulmonary drug delivery systems. By leveraging the unique properties of Nanoemulsions, SNEDDS optimizes drug absorption and therapeutic efficacy in these diverse applications.

Applications of Nano emulsions in Drug Delivery (60)

Nanoemulsions (SNEDDS) are widely utilized in drug delivery, impacting areas like cosmetics, transdermal drug systems, cancer therapy, and vaccine delivery. They also enhance cell culture technology, improve the oral bioavailability of poorly soluble drugs, and support ocular and otic delivery systems. Additionally, Nanoemulsions are effective in intranasal, parenteral, and pulmonary drug delivery, offering versatile solutions for efficient drug administration.

Protection against Biodegradation (60)

SNEDDS, along with similar systems such as SMEDDS and SEDDS, is crucial for the effective delivery of macromolecules; including peptides, hormones, and enzyme substrates, while providing robust protection against enzymatic degradation. This capability is vital for ensuring the stability and bioactivity of sensitive compounds, thereby enhancing their therapeutic potential. The protective mechanisms afforded by these delivery systems not only preserve the integrity of active ingredients but also promote their efficacy in clinical applications, making SNEDDS an indispensable tool in modern pharmaceutical formulations.

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