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Review Article

REVOLUTIONIZING PHARMACEUTICALS: A DEEP DIVE INTO SELF NANO EMULSIFYING DRUG DELIVERY SYSTEMS

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ABSTRACT

From nearly a decade's time, there has been an increased inclination with respect to nanoemulsions owing to their augmented and ameliorated characteristics in comparison to conventional methods of drug delivery. Self-nano-emulsifying drug delivery systems (SNEDDS) have substantiated their effectiveness in enhancing the solubility and bioavailability of poorly soluble substances. These systems, often isotropic mixtures, consist of oils, surfactants, and cosurfactants/cosolvents. They possess the capability to create nanoemulsions or fine oil-in-water (o/w) emulsions with mild stirring and dilution by the water phase along the gastrointestinal tract. This system has proven its worth in enhancing the absorption of lipophilic agents constrained by dissolution rate. SNEDDS are extremely efficacious in improving the oral bioavailability of lipophilic products and is quite promising for managing drugs unapt for oral delivery. Additionally, it's noteworthy that SNEDDS can be formulated into various solid dosage forms suitable for both oral and parenteral administration. This overview incorporates the advancements of SNEDDS' the mechanism involved in its spontaneous formation, its subcategories, composition, approaches employed for formulation, characterization, merits and limitations, and future potential. The review also lays stress on the progress in solid self-emulsifying delivery mechanisms and dosage forms.

Keywords: SNEDDS, Self-nanoemulsifying drug delivery, Formulation, Mechanism, Formulation techniques, *In vitro* lipolysis, Solidification techniques, S-SNEDDS, Solid self-nanoemulsifying drug delivery, SMEDDS, SEDDS, Spontaneous emulsification, Lipid based formulation.

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INTRODUCTION

The advancement in the field of combinatorial chemistry and screening techniques has led to the discovery of novel chemical compounds. However, the increased use of these technologies has shifted the focus of screening toward identifying lead compounds with higher molecular weight and greater lipophilicity. Unfortunately, this shift has resulted in the development of compounds with poor solubility in aqueous solutions. Solubility is a critical factor in determining the effectiveness of oral medications [1].

In recent years, there has been a significant increase in the discovery of such drugs which possess low solubility. According to the Biopharmaceutics Classification System (BCS), many drugs fall into BCS class II and class IV where in BCS class II drugs have poor aqueous solubility and BCS class IV drugs have both poor solubility and permeability. This limitation hampers their absorption and leads to inefficient use of medical resources. Surprisingly, over 50% of newly developed drugs are lipophilic, exhibit poor aqueous solubility and have low bioavailability [2, 3].

For researchers and scientists, the most pressing challenge lies in formulating these poorly soluble drugs effectively. Many researchers have successfully developed many formulations and delivery systems to enhance the solubility and permeability of lipophilic drugs. These include liposomes, niosomes, polymeric micelles, nanoparticles, nanoemulsions, microsponges, cubosomes, aquasomes, ethosomes, resealed erythrocytes, microspheres and inorganic nanoparticles. Among other delivery systems, lipid-based drug delivery systems have exhibited significant potential for improving the oral bioavailability of lipophilic drugs, in addition to proteins and nutrients [4, 5].

These lipid-based nanocarriers include various alternatives, such as solid lipid nanoparticles, liposomes, nanoemulsions, lipid-core micelles, drug lipid conjugates and self-nanoemulsifying drug delivery systems (SNEDDSs). In comparison to conventional lipid-based drug delivery systems, SNEDDSs have demonstrated appreciable increments in the solubility and oral bioavailability of hydrophobic drugs, particularly those classified under BCS classes II and IV. This is attributed to their more consistent physicochemical characteristics and lower surface free energy [6, 7].

SNEDDSs, which belong to the category of lipid-based drug delivery systems, consist of uniform mixtures comprising drugs, oils, surfactants and cosurfactants. Typically, SNEDDSs can spontaneously create nanoemulsions with droplets smaller than 200 nm when they come into contact with an aqueous solution under mild agitation. Notably, SNEDDS formulations like Sandimmune (containing cyclosporine), Norvir (containing ritonavir), Fortovase (containing saquinavir) and Neoral (also containing cyclosporine) have demonstrated impressive effectiveness [8, 9].

To address challenges and offer advantages, solidified SNEDDSs have been developed to transform liquid or semisolid components into powders using various solidification techniques like adsorption, spray drying, melt granulation, extrusion-spheronization, eutectic mixing and capsule filling. In comparison to regular SNEDDSs, these solidified self-nanoemulsifying drug delivery systems (S-SNEDDSs) offer several benefits, including simpler manufacturing processes, more stable dosage forms and enhanced patient compliance [6, 7].

Both SNEDDSs and S-SNEDDSs play a significant role in enhancing the absorption and transport of poorly permeable drugs. They achieve this by reducing the activity of intestine efflux transporters, protecting drugs from degradation in the body, and facilitating drug absorption through the intestinal lymphatic pathway. Moreover, these systems minimize the leaching of poorly water-soluble drugs from tiny oily droplets into the aqueous medium during storage. Considering these advancements, we have summarized recent progress in the development and application of SNEDDS and S-SNEDDS in this review.

Mechanism of SNEDDS

Self-nanoemulsifying drug Delivery Systems spontaneously form with droplets smaller than 200 nm in size. The process of spontaneous emulsification involves numerous mechanisms that are influenced by factors like the system's composition, physicochemical properties and the specific emulsification method used. During this

formation process surfactants arrange themselves at the interface between oil and water in order to reduce interfacial tension. Therefore, oil, surfactant, cosurfactant, and drug all play critical roles in creating a stable SNEDDS. A comprehensive understanding of the mechanism behind SNEDDS formation is essential for the rational design of desired SNEDDS formulations [10].

As the droplet size in an emulsion decrease, the interfacial surface area increases. Typically, surfactants reduce the surface tension of emulsions by localizing at the oil-water interface. Small cosurfactant molecules enhance the emulsification process by penetrating the surfactant layer at the oil-water interface further reducing.

interfacial tension and facilitating the formation of fine droplets [11]. To achieve a stable SNEDDS formulation, it is important that the free energy required is strongly negative. Surfactants and cosurfactants in SNEDDS act as a mechanical barrier against coalescence [12]. According to the thermodynamic theory of emulsion formation, the free energy of SNEDDS formation can be expressed as follows:

$$\Delta G = \gamma \Delta A - T\Delta S$$

In this equation, "ΔG" represents the interfacial tension at the oil-water interface, "ΔA" signifies the change in an interfacial area, "T" denotes temperature, and " S" reflects the change in dispersion entropy. Researchers such as Lawrence and Rees have noted that the significant increase in interfacial area is due to the formation of numerous small droplets. They have proposed that the composition and concentration of surfactants are crucial in reducing the free energy of formation, simultaneously increasing the system's dispersion entropy and reducing interfacial tension. Increasing the volume of surfactant in a SNEDDS leads to more favourable nanoemulsion formation which is associated with enhanced stability and suggests a lower free energy of formation. The thermodynamic treatment of conventional emulsion formation as described by Reiss, reveals that the free energy required is directly related to the energy needed to create a new surface between the phases. This can be expressed as:

$$\Delta G = \sum 4N\pi r^2\sigma$$

In this equation, "ΔG" represents the free energy, "N" stands for the number of droplets, "r" indicates the radius of droplets, and "σ" represents the interfacial energy. It is evident from this equation that the lower the interfacial energy lowers the total free energy of the system. When oil, surfactant and cosurfactant are mixed with water under gentle agitation, an interface forms between the two phases. Subsequently, water infiltrates this interface reaching the oil phase up to its solubilization limit. Increased water penetration leads to the formation of a dispersed liquid crystalline phase which is influenced by the concentration of surfactant. Mild agitation of SNEDDS induces rapid water penetration, disrupting the interface and resulting in the formation of emulsion droplets [13].

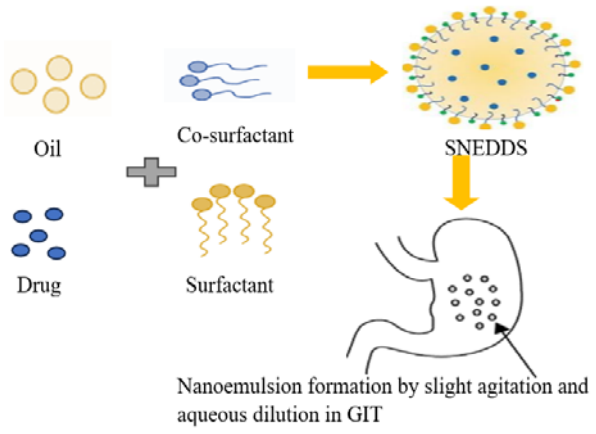

Fig. 1: Mechanism of SNEDDS

Factors influencing the performance of SNEDDS

Nature and dose of drug

High-dose drugs may not be suitable for self-emulsifying drug Delivery Systems (SNEDDS) unless they have excellent solubility, particularly in the lipophilic phase. Drugs with low solubility in both water and lipid are typically indicated by log P values around 2 and poses significant challenges for SNEDDS delivery. The ability of SNEDDS to keep the drug in a dissolved form is strongly affected by the drug's solubility in the oil phase. If the drug's solubility relies heavily on surfactants or co-surfactants, there is a risk of precipitation when the SNEDDS is diluted because the solvent capacity of these agents decreases.

Equilibrium solubility tests are employed to predict potential instances of precipitation in the gastrointestinal tract. However, crystallization may proceed slowly in the complex, solubilizing and colloid-stabilizing environment of the gut. The need for practical methods to anticipate the fate of drugs following the dispersion of lipid systems in the gastrointestinal tract is evident [14].

Polarity of the lipophilic phase

The release of drugs from nanoemulsions is influenced by several factors one of which is the polarity of the lipid phase. The polarity of the droplets is determined by multiple factors, including the Hydrophilic-Lipophilic Balance (HLB), the chain length and degree of unsaturation of the fatty acids and the molecular weight of micronized components which can inhibit crystallization and maintain a supersaturated state for an extended duration.

Selection of the appropriate emulsifying system (Surfactant)

Choosing the right surfactant is crucial for achieving ultra-low interfacial tension. This is essential to create a stable nanoemulsion system. The surfactant helps in reducing the interfacial tension between the dispersed and continuous phases enabling the formation of small and stable droplets in the nanoemulsion.

Solubility of the dispersed phase

The drug or active ingredient in the dispersed phase should have extremely low solubility in the continuous phase (typically water). This is important to prevent Ostwald ripening a phenomenon where larger droplets grow at the expense of smaller ones over time leading to instability and phase separation in the nanoemulsion.

Optimal surfactant concentration

To maintain the stability of the nanoemulsion the surfactant must be used at its optimum concentration. The surfactant molecules form a protective layer around the droplets preventing coalescence and ensuring long-term stability. Using too much or too little surfactant can affect the stability and performance of the SNEDDS.

These factors are essential for the successful design and formulation of SNEDDS which is a valuable approach for enhancing the solubility, bioavailability and overall performance o poorly water-soluble drugs and active compounds [14].

Composition of SNEDDS

The self-emulsification process relies on:

- The characteristics of the oil and surfactant.
- The amount of surfactant present.
- The temperature at which self-emulsification takes place.

Oils

The choice of oil is a critical component as it plays a key role in facilitating the formation of self-microemulsion. Oils enable the solubilization of lipophilic drugs leading to increased drug transport through the intestinal lymphatic system and enhanced drug absorption. Hydrogenated vegetable oils are often used as the base for lipid-based delivery systems. They are generally safe for consumption as they are fully digested and absorbed without any significant safety issues [15]. Vegetable oils derived from various

sources contain different proportions of fatty acids. For instance, coconut oil can be subjected to distillation to produce "medium-chain triglycerides" (MCT), which consist mainly of saturated C8 (50–80%) and C10 (20–45%) fatty acids. Castor oil is another common source, containing Glyceryl ricinoleate, which is unique due to the hydroxyl group linked to the alkyl chain [15].

Surfactants

The choice of surfactant and its concentration range plays a crucial role in the formation of nanoemulsion. The surfactant serves to reduce the interfacial tension, and the gentle agitation resulting from the digestive motility of the stomach and small intestine is adequate to achieve microemulsion formation. While many compounds exhibit surfactant properties and are used in designing self-nanoemulsifying systems the selection of surfactants for oral use is limited, with considerations mainly focusing on two key parameters: hydrophilic-lipophilic balance and safety [16]. Ideally, surfactants should have a high HLB value. Non-ionic surfactants with a relatively high HLB are widely accepted for microemulsion formation. Some of the most employed emulsifiers/surfactants include various solid or liquid ethoxylated-polyglycolized glycerides and polyoxyethylene 20 oleate, such as Tween 80.

The safety of the chosen surfactant is a critical factor during the selection process. Typically, surfactant concentrations range between 30% and 70% w/w to form stable SNEDDS.

SNEDDS formation is favored when lipid mixtures have higher surfactant and co-surfactant/oil ratios [17].

Cosurfactant

To create the most effective SNEDDS it is essential to use relatively high surfactant concentrations, typically exceeding 30% w/w. However, when surfactants are present in high concentrations, they can potentially lead to irritation in the gastrointestinal tract and even cause toxicity. To mitigate this issue, the concentration of surfactants can be reduced by incorporating a co-surfactant into the formulation. The careful selection of both the surfactant and co-surfactant is a critical step, not only for achieving SMEDDS formation but also for ensuring the successful solubilization of the drug within the SMEDDS [18].

Formulation techniques of liquid SNEDDS

Numerous techniques have been developed to produce nanoemulsions. Nevertheless, the generation of a nanoemulsion system demands a substantial input of energy, which can be achieved through mechanical equipment or by utilizing the inherent properties of the constituents. Below are some of the methods employed in the formulation of a self-nanoemulsifying drug delivery system.

High energy approach

Creating a nanoemulsion requires the application of significant energy. This process primarily hinges on the specific mixture composition, which includes surfactants, co-surfactants, co-solvents and other functional compounds. Mechanical treatment is employed in the emulsification process to generate the nanoemulsion. These include High Pressure Homogenization (HPH), microfluidization and ultrasonication methods.

High-pressure homogenization

This technique holds significant importance in both detecting and creating fine emulsions particularly to produce nanoemulsions. This technique involves subjecting the oil/water surfactant mixture to very high pressure and propelling the mixture through a resistive valve. The generation of extremely small emulsion droplets is attributed to the exceptionally high shear stress in this process. The reduction in droplet size during homogenization is explained by a combination of two principles: Turbulence and Cavitation. The resulting mixture attains high velocity within the homogenizer valve, creating intense turbulent eddies of the same size as the mean diameter of a droplet (MDD). The eddies effectively disperse the droplets and reduce their size. Additionally, as the mixture passes through the valve and undergoes a pressure drop, cavitation occurs, introducing further disruptive eddies that further break down the droplets. Reducing the gap size in the valve leads to increased pressure on the droplets, resulting in a greater degree of cavitation. With enough surfactant to completely cover the oil-water interface and high adsorption kinetics it becomes possible to produce emulsion droplets with diameters smaller than 100 nanometers using this method. This is crucial for preventing droplet coalescence [19].

Fig. 2: High pressure homogenization

Microfluidization

Microfluidization is another important technique for detecting and preparing nanoemulsions. This process is achieved using a device known as a microfluidizer. This device incorporates a high-pressure positive displacement pump (500-300 PSI) that forces the product through an interaction chamber containing small channel droplets, referred to as microchannels. The product flows through these microchannels into an impingement area, resulting in the creation of very fine particles in the submicron ranges. To achieve these, two solutions containing a mixture of aqueous phase and oil phase are combined and formed into a coarse emulsion within an inline homogenizer. This coarse emulsion is then further processed using a microfluidizer to produce a homogeneous, transparent, and stable nanoemulsion [20].

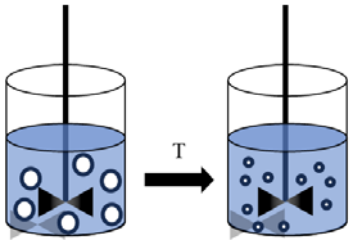

Fig. 3: Microfluidization

Ultrasonication method

Ultrasonication is a highly efficient method for reducing droplet size in emulsions. In this technique, specialized devices often referred to as Sonicator probes are used to impart energy. These probes may contain quartz crystals that respond to alternating electric energy by undergoing expansion and contraction or they can employ piezoelectric crystals.

When the tip of the Sonicator probe comes into contact with a liquid it initiates mechanical vibration and cavitation. Cavitation involves the formation and subsequent collapse of tiny bubbles within the liquid. This process directly leads to the creation of an emulsion. Through ultrasonication, emulsion droplets as small as 0.2 mm can be produced, making this method particularly valuable for laboratory-scale applications [21].

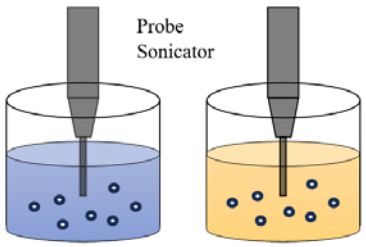

Fig. 4: Ultrasonication method

Low energy approach

The low-energy approach, also known as the condensation method, requires minimal energy for the production of nanoemulsions. It relies on phase transitions occurring during the emulsification process and is heavily dependent on the modulation of interfacial phenomena, phase transitions and the intrinsic physicochemical properties of surfactants, co-surfactants and oil to create nano-sized emulsion droplets. This method utilizes the stored energy of the system to generate smaller droplets and can be induced by changes in parameters like temperature and composition that may affect the hydrophilic-lipophilic balance (HLB) of the system [20]. Methods categorised under low energy approach include Phase Inversion Temperature (PIT) method, solvent displacement method, phase inversion composition method and spontaneous emulsification method.

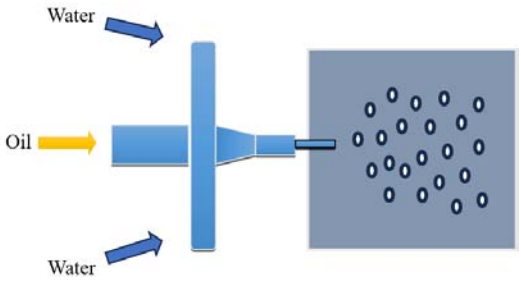

Fig. 5: Low energy approach

Phase inversion temperature (PIT) method

The PIT method is crucial for preparing both nanoemulsions and microemulsions. It relies on temperature responsiveness, leading to various physical changes, including physicochemical alterations, changes in particle size and *in vivo* and *in vitro* drug release rates. Non-ionic surfactants are responsive to temperature changes and transitioning from O/W nanoemulsions at lower temperatures to W/O nanoemulsions at higher temperatures.

Solvent displacement method

The solvent displacement method for spontaneous nanoemulsion creation is adapted from the nano-precipitation method used in polymeric nanoparticles. This approach involves dissolving the oily phase in water-miscible organic solvents like acetone, ethanol, or ethyl methyl ketone. The organic phase is introduced into an aqueous phase containing a surfactant, resulting in the rapid formation of nanoemulsion due to the quick diffusion of the organic solvent. Subsequently, the organic solvent is removed from the nanoemulsion using methods such as vacuum evaporation [22].

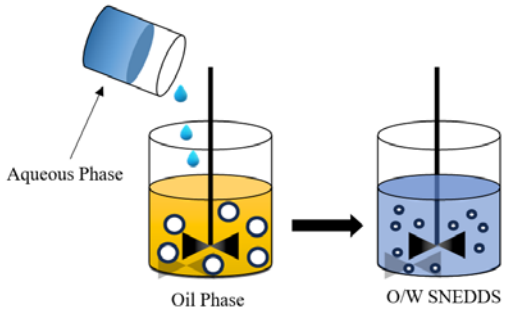

Fig. 6: Phase inversion composition method

Phase inversion composition method

This method enables the production of nanoemulsions at room temperature without the use of organic solvents or heat. It has been observed that kinetically stable nanoemulsions with smaller droplet sizes (around 50 nm) can be generated by incrementally adding water into a solution of surfactant in oil with gentle stirring while maintaining a constant temperature. While the components used in the initial study were not of pharmaceutical grade, this approach has opened doors for designing pharmaceutically acceptable nanoemulsions using a similar methodology [23].

Spontaneous emulsification

In spontaneous emulsification the formation of nanoemulsion occurs spontaneously. This process begins with the preparation of a uniform and consistent organic solution comprising a hydrophilic surfactant phase, a water-miscible surfactant, as well as oil and a lipophilic surfactant. Subsequently, the organic phase is gently introduced into the aqueous phase while maintaining continuous magnetic stirring. This results in the creation of a stable o/w emulsion. The aqueous phase is then removed via evaporation under reduced pressure [24].

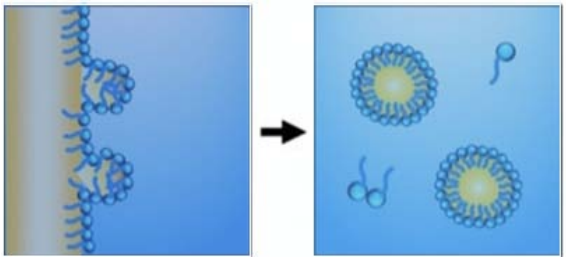

Fig. 7: Spontaneous emulsification

Optimization parameters

Percent transmittance

Percent transmittance represents the amount of light transmitted. The interpretation of transmittance results is based on the visual clarity of the sample. A formulation that is exceptionally clear will yield a high percent transmittance, typically ranging from 80% to 100%. When analysing SNEDDS samples, percent transmittance serves as a valuable indicator of the uniform mixing of the SNEDDS formula resulting in droplets of nanometre size, generally less than 200 nm and a visibly clear and transparent appearance.

This test is a critical factor in assessing the physical attributes of the nanoemulsion system created within SNEDDS formulations. It is an integral component of the quality parameters used to characterize SNEDDS preparations. Achieving a high transmittance value is important as it enhances the surface area, facilitating the rapid release and absorption of drugs in the gastrointestinal tract. For SNEDDS, an excellent transmittance value typically exceeds 80%. To determine percent transmittance a UV-Vis spectrophotometer is employed at a specific wavelength of 650 nm. If the percent transmittance of a sample closely approaches the transmittance value of distilled water, which is set at 100%, it is considered to possess a level of clarity similar to that of water [25].

Emulsification time

The emulsification time test evaluates how quickly SNEDDS can create nanoemulsions when exposed to stomach's intestinal fluids. A key requirement for SNEDDS is the ability to swiftly form nanoemulsions through gentle stirring. The selection of oil, surfactant, and co-surfactant in the SNEDDS formula plays a pivotal role in facilitating emulsification within the gastrointestinal tract. The faster the emulsification time, the greater the drug absorption. A successful emulsification time test indicates that SNEDDS can generate a clear and transparent nanoemulsion within 1-2 min.

Viscosity

Viscosity testing serves the purpose of gauging a liquid's resistance to flow. It is a measure of the difficulty in the relative motion of fluid

components. The greater the viscosity of a liquid, the more challenging it is for the liquid to move.

Droplet size

In pharmaceutical formulations employing SNEDDS it is essential for particle sizes to be below 200 nm. This ensures that SNEDDS can function effectively as a drug delivery system characterized by both clarity and stability. The presence of small particles in the SNEDDS formulation becomes evident when conducting percent transmittance tests. Additionally, the small particle size aids in preventing sedimentation, contributing to enhanced stability. This test employs a particle size analyser (PSA) instrument.

Dispersibility test

The dispersibility test for SNEDDS evaluates its capacity to blend into an emulsion and determines the size of resulting globules, a crucial aspect in categorizing them as SNEDDS. This examination is conducted using a standard USP paddle-type dissolution test apparatus. In this test a 500 ml volume of water at a temperature of 37±0.5 °C is employed and a paddle is set in motion rotating at a speed of 50 rpm. By systematically adding water, the SNEDDS formulation interacts to form a mixture with varying characteristics. This procedure permits the evaluation of the *in vitro* performance of the formulation contingent on the nature of the resultant mixture.

During titration with water, the SNEDDS formulation forms a mixture or gel of different types, leading to the assessment of the *in vitro* performance through a grading system:

Grade A: Rapidly forms a nanoemulsion within 1 minute, appearing clear or bluish.

Grade B: Rapid formation, with a slightly less clear emulsion and a bluish-white appearance.

Grade C: Forms a fine milky emulsion within 2 min.

Grade D: Yields a dull, greyish-white emulsion with a slightly oily appearance that emulsifies slowly (more than 2 min).

Grade E: The formulation displays poor or minimal emulsification, characterized by large oil globules on the surface.

Formulations falling within Grade A and Grade B will retain their nanoemulsion state when dispersed in the gastrointestinal tract (GIT). In contrast, formulations categorized under Grade C are recommended for SNEDDS formulations. It's worth noting that the stability of the formulation diminishes as it transitions from a microemulsion to an emulgel state [26].

Morphological study

Conducting a morphological study is crucial for obtaining information regarding the external attributes of the formulation. This encompasses aspects such as colour, Odor, consistency, density and overall appearance. In the context of a Self-Nanoemulsifying Drug Delivery System (SNEDDS), the study involves the observation of globules through a transmission electron microscope (TEM). Samples are observed and evaluated to provide information about the formulation's characteristics.

pH measurements

The pH of nanoemulsion formulation can be recorded using a pH meter or potentiometer. Electrodes are completely immersed in either semisolid or liquid formulations, and the pH is measured.

Small-angle x-ray scattering measurement (SAXS)

Small-angle X-ray scattering (SAXS) is a tool employed to determine the size distribution of nanoparticles, for evaluation of the size and configuration of monodisperse macromolecules and to quantify the pore size and characteristic length of partially ordered structures. In recent times, researchers have applied SAXS to investigate the phase structure and liquid crystalline organization of SNEDDSs.

Crystallization of drugs

X-ray diffraction (XRD) can be used to determine the crystallization of drugs within SNEDDSs and S-SNEDDSs.

***In vitro* lipolysis**

In vitro lipolysis is a technique used for determining enzymatic degradation and understanding how SNEDDSs facilitate drug delivery. *In vitro* lipolysis procedure is usually carried out in a thermally controlled reaction vessel, which contains a digestive medium that mimics either the fasted or fed states. This medium usually comprises an aqueous buffer solution supplemented with bile salts (BSs), phospholipids (PLs), and sodium chloride (NaCl).

Drug-release studies

The capability of SNEDDS and S-SNEDDS formulations in enhancing the solubility and bioavailability of hydrophobic drugs along with protecting them from enzymatic degradation, has proven highly efficacious. It is important to emphasize that the rate of drug release from a SNEDDS is affected by factors such as droplet size, drug solubility and release conditions. Generally, *in vitro* drug release from a SNEDDS preparation occurs more rapidly in comparison to free drug formulations.

Refractive index

The refractive index serves as a valuable measurement for determining the transparency of a formulation. It can be evaluated using a refractometer by placing a drop of the solution on a slide and then comparing it with water. The formulation is transparent in nature if the refractive index of the system has value equivalent to that of water.

Scanning electron microscopy (SEM)

The surface characteristics of solid-SMEDDS samples are examined through Scanning Electron Microscopy (SEM). This involves sprinkling the sample onto an aluminium substrate, followed by the application of a coating of gold particles in a high vacuum environment at an accelerating voltage of 10 KV.

***In vitro* permeation studies**

Two commonly employed methods for *in vitro* assessment of drug permeation are the parallel artificial membrane permeability model (PAMPA) and the Caco-2 cell model. PAMPA, known for its high-throughput capabilities, relies on an artificial lipidic membrane to predict the passive oral absorption of drugs. In this method, the drug is initially placed in the donor compartment, while the apical compartment remains drug-free. Following a designated incubation period, the quantity of drug that has passed through is determined for each compartment. These compartments may also contain supplementary substances to facilitate drug binding during the permeation process. PAMPA is particularly advantageous in early-stage drug development due to its ease of automation, cost-effectiveness and compatibility with high-capacity solubilizers [27].

Advantages of self-nanoemulsifying drug delivery systems

- Enhanced solubility and bioavailability with reduction in dosing frequency: SNEDDS are known to improve the solubility of poorly water-soluble drugs hence making them more bioavailable. This is particularly important for drugs with low aqueous solubility as SNEDDS can increase their therapeutic efficacy. It also helps in reducing the dosing frequency with decrease in the number of capsules or tablets being consumed. Hence it improves patient compliance as it allows patients to stick to their therapeutic regimen [25].

- Improved drug stability: SNEDDS offers enhanced drug stability by protecting them from degradation and hydrolysis reactions, thereby extending their shelf life. This is achieved by encapsulating drugs within nano-emulsion droplets. This feature is of prime importance when it comes to peptide drugs which are vulnerable to enzymatic breakdown in the gastrointestinal tract. By being encapsulated in an oil droplet, the drug derives protection against hydrolysis and oxidation. Furthermore, this entrapment of the drug can also serve as a taste-masking mechanism, thereby improving palatability of drug [28].

- Enhanced absorption: Due to their sizes being in the range of 10-200 nm, the nano-sized droplets in SNEDDS possess a large surface

area. Hence, they can contribute to improve absorption of drug in the gastrointestinal tract. This modification leads to a quicker onset of action and more predictable pharmacokinetics.

- Reduced Variability in Pharmacokinetics: SNEDDS can minimize the inter-and intra-subject variability in drug absorption. This is crucial in cases where the drugs have a narrow therapeutic index wherein maintaining consistent blood levels of drug are critical.

- Reduced food effect: Certain orally administered drugs show hindered absorbance in presence of food. Hence to overcome this issue, the drug can be formulated as SNEDDS since SNEDDS can be designed to be less affected by presence of food. This can improve patient compliance and comfort.

- Precise dosing: SNEDDS can be formulated to administer an exact known quantity of drug (precise dose) hence making it easier to control and predict the release and absorption of the drug.

- Flexibility in drug formulation: SNEDDS can be employed for various types of drug candidates, including hydrophobic and hydrophilic compounds, making it a competent drug delivery system.

- Potential for reduced side effects: The ability to use lower doses of drugs while maintaining therapeutic efficacy can reduce the risk of untoward adverse effects and toxicity.

- Faster onset of action: SNEDDS can lead to a quicker onset of action due to improved drug solubility and absorption.

- Reduced interactions with other medications: SNEDDS can minimize drug interactions that may occur when multiple medications are taken simultaneously. This is possible only because SNEDDS keep drug in an encapsulated form, hence preventing drug-drug interactions.

- Targeted drug delivery: With appropriate modifications, SNEDDS can be designed for targeted drug delivery to specific sites in the body, such as colon, tumour sites, etc.

- Superior physical stability: Stability is a prominent feature of this system as it prevents flocculation, aggregation, creaming and coalescence due to its inherent thermodynamic and kinetic stability. This inherent stability ensures that the system remains thermodynamically stable over an extended period without experiencing creaming or phase separation [14].

- Easy manufacturing process: The process of manufacturing and scaling up SNEDDS is characterized by its simplicity and ease. In contrast to typical emulsion-based systems, SNEDDS do not necessitate a high degree of agitation for microemulsion formation. This ease of manufacturing and scaling up is a pivotal advantage that sets SNEDDS apart from other drug delivery systems such as solid dispersions, liposomes and nanoparticles. SNEDDS can be produced in straightforward and cost-effective facilities, using basic equipment like mixers with agitators and volumetric liquid filling machines for large-scale production [29].

Disadvantages of self-nanoemulsifying drug delivery systems

- Stabilization of SNEDDS requires a high concentration of surfactants/co-surfactants (30-60%), which can potentially cause toxicity problems.

- The stability of the Self-nanoemulsifying drug delivery system can be influenced by change in temperature and ph. Change in temperature may cause Oswald ripening which can lead to instability.

- The effectiveness of SNEDDS in maintaining the drug in a solubilized state depends significantly on the drug's solubility in the oily phase, but it can possess a higher risk of drug precipitation if surfactants or co-surfactants play a prominent role in drug solubilization [31].

- In SNEDDS, the presence of oil can introduce unwanted odours or tastes, potentially leading to patient noncompliance.

- L-SNEDDS leads to form bulkier dosage forms as compared to solid oral dosage, which could present challenges for storage, handling and transportation.

- L-SNEDDS can be incorporated into unit dosage forms like soft gelatine or HPMC capsules, but it can adversely affect the capsule shell by causing softening or hardening and cause drug leakage, which is undesirable for long-term storage

- Higher manufacturing cost due to use of sophisticated instruments during manufacturing and droplet size reduction can lead to an increase in product cost.

- Conventional dissolution methods may not be suitable for evaluating SNEDDS formulations since they may be dependent on digestion before drug release and there are currently no reliable predictive *in vitro* models available for assessment [30].

Limitations of liquid snedds

Liquid self-nanoemulsifying drug delivery systems (L-SNEDDS) are generally administered using soft or hard gelatine capsules or HPMC capsules. However, there are several issues associated with delivering these systems in capsules over the long term. These problems include the potential incompatibility of system components with the capsule shell, drug precipitation during manufacturing, storage at lower temperatures and the requirement for precise production methods [31]. Furthermore, SNEDDS may not be suitable for hydrophobic drugs that are prone to pH-catalysed or solution-state degradation. Additionally, liquid SNEDDS (L-SNEDDS) come with several limitations, including the potential for drug-drug and drug-excipient interactions, drug precipitation at low temperatures, increased production costs, complex manufacturing processes, issues related to taste and palatability and handling concerns [32]. Modified oily phases used for SNEDDS fabrication have acidic pH due to the presence of traces of free fatty acids. These acids can catalyse the degradation of pH-sensitive drugs such as cefpodoxime proxetil on long-term storage. It can be observed that Cefpodoxime Proxetil undergoes hydrolysis to a completely insoluble product (cefpodoxime acid) on 3 mo of storage as per the ICH guidelines. Researchers have observed that simvastatin SNEDDS formulation was susceptible to hydrolytic degradation at accelerated conditions of storage owing to reactive ester and lactone moiety. The researchers recognized that the challenges associated with handling, manufacturing, and stability of liquid SNEDDS could potentially be addressed by transforming them into a solid form. This led to the development of the concept of solid SNEDDS. Solid SNEDDS, in the form of dry, powdered substances, offer a solution to the limitations often encountered with liquid SNEDDS. Solid dosage forms are not only more stable but also easier to handle. Consequently, efforts have been directed towards converting liquid systems into solid SNEDDS.

Formulation techniques of solid self-nanoemulsifying drug delivery systems (S-snedds)

Spray drying

In this method, the preparation of the formulation involves blending lipids, surfactants, the drug, solid carriers, and the solubilization of these mixtures before proceeding to the spray drying phase. The solubilized liquid formulation is atomized into droplets and introduced into a drying chamber where the volatile phase (e. g., water in an emulsion) evaporates under controlled temperature and airflow conditions, resulting in dry particles. Various solid carriers, such as Dextran 40 (a water-soluble solid carrier) and Aerosil® 200 (a non-porous and hydrophilic solid carrier), have been employed for the preparation of S-SNEDDS. Critical parameters of the spray drying system include inlet and outlet air temperatures, viscosity, solid content, surface tension, feed temperature, volatility of the solvent and nozzle material. This method has varied applications ranging from aseptic pharmaceutical processing to ceramic powder production. It is a rapid process and is available in various designs to meet specific product requirements. This method can be used for both heat-resistant and heat-sensitive products. It allows precise control over particle size, bulk density, crystallinity, organic volatile impurities, and residual solvents. The main drawback of the method includes overall low thermal efficiency as a large volume of heated air may not directly contact particles during drying. The equipment involved in this method is also expensive and bulky, thereby increasing maintenance costs and posing difficulty in shipment [33].

Adsorption to solid carriers

This method involves transforming liquid self-nanoemulsifying formulations into free-flowing powders through adsorption onto solid carriers. The process includes mixing the liquid formulations with carriers in a blender, resulting in a powdered form that can be filled directly into capsules or used to formulate tablets. Solid carriers like Neusilin US2, Avicel PH 101, and spray-dried lactose are commonly used. This method ensures good content uniformity [29].

Capsule filling with liquid and semisolid self-emulsifying formulation

Capsule filling is an economical and prevalent technique for encapsulating liquid or semisolid self-emulsifying formulations for oral administration. For semisolid preparations, the process involves four steps: heating semisolid excipients above their melting point, incorporating active substances, filling capsules with molten material, and cooling to room temperature. For liquid formulations, the process consists of filling liquid formulation into capsules and sealing the capsule body and cap through banding or micro spray sealing. It is a simple process and is suitable for low-dose and highly potent drugs. High drug loading potential is another key feature of this method.

Melt extrusion/Extrusion spheronization

Melt extrusion is a solvent-free process involving the conversion of raw materials with plastic properties into uniformly shaped and dense products by forcing them through a die under controlled conditions of temperature, product flow, and pressure. Extrusion spheronization consists of dry mixing active ingredients and excipients to form a homogeneous powder, extruding this mixture into a spaghetti-like extrudate, spheronizing the extrudate into uniform-sized spheroids, dry sifting to achieve the desired size distribution, and applying a coating [36]. This method, like the previous one, also facilitates high drug loading (up to 60%). It ensures good content uniformity, with short processing time and simple equipment [34].

Dry emulsions

Dry emulsions are powders that spontaneously form emulsions *in vivo* or when exposed to an aqueous solution. These dry emulsions can be used for tablet or capsule preparation. They are typically prepared from oil/water emulsions containing a solid carrier (such as lactose or maltodextrin) in the aqueous phase through methods like rotary evaporation, freeze-drying, or spray drying [35].

Supercritical fluid-based technique

This approach utilizes lipids, often supercritical carbon dioxide to either coat drug particles or create solid dispersions.

Solid lipid nanoparticles and nanostructured lipid carriers (SLN and NLC)

SLN and NLC are submicron-sized particles, typically ranging from 50-1000 nm composed of physiologically tolerated lipid components. They are prepared by high-pressure homogenization of a solid lipid matrix and drug using aqueous solutions containing surfactants. SLN and NLC are often employed for controlled-release applications in various administration routes [36].

Cryogenic grinding

This method is particularly suitable for formulations containing Gelucire® 44/14 as a self-emulsifying excipient. Cryogenic grinding is used to form solid dosage forms like tablets and pellets from semi-solid formulations, as Gelucire has a low melting point [37].

Self-solidification by surfactant

Primarily used for formulations containing Gelucire® 44/14 as a surfactant, this technique involves preparing a mixture of oil, surfactant, and co-surfactant and allowing it to solidify at room temperature or through freezing. Gelucire possesses both surfactant properties and the ability to solidify the mixture [38].

Pour moulding

The pour moulding method is a technique used to create self-emulsifying suppositories and tablets. To employ this method, oil and surfactant are combined and heated until they achieve complete homogenization. The drug is then added to this uniform mixture and thoroughly stirred. Subsequently, the resulting mixture is poured into molds and allowed to set at a temperature of 4 °C. The tablets or suppositories with self-emulsifying properties are removed from the moulds and stored in a cool location [39].

Spray congealing

In the spray congealing process, self-emulsifying microparticles are produced using spray congealing technology. This method employs fluidized bed equipment with two fluid atomizers featuring wide orifice openings, such as pneumatic nozzles. External mixing of fluid and air or gas takes place outside the nozzle orifice, enabling atomization to be adjusted by altering the air pressure without affecting the liquid flow rate. The temperature of the feed tank, containing molten fluid, should be maintained above the melting temperature. A refrigeration system in the congealing chamber is used for the solidification of droplets [40].

Melt granulation

Melt granulation is a one-step method for preparing S-SEDDS. It eliminates the need to first create L-SEDDS and then adsorb them onto a solid carrier. In this method, solid oils like goat fat or surfactants that are solid at room temperature are utilized. The oil and surfactant mixture are heated above their melting point, and the drug is added and mixed to form a homogeneous blend [41].

Lyophilization

Lyophilization, or freeze-drying, can also be employed to formulate S-SEDDS. This process involves the direct evaporation of water through sublimation and includes several steps: freezing, primary drying, and secondary drying. In this method, both the carrier and L-SEDDS are dissolved in a common solvent, followed by freezing and sublimation processes. The result is a solid product [4].

Advancements in snedds

Controlled-release solid SNEDDS

SNEDDS pharmacokinetics properties, like conventional oral formulations, result in rapid absorption, leading to a high Cmax and a low Tmax. This can cause fluctuations in plasma drug concentration, necessitating close monitoring. To address this issue, controlled-release SNEDDS have been developed, providing sustained and controlled-release properties without compromising bioavailability. Controlled-release SNEDDS offer improved bioavailability, a lower Cmax, an extended mean residence time (MRT), a delayed Tmax, and reduced plasma drug fluctuations. Controlled drug release is achieved by releasing reconstituted nano-sized emulsions at a zero-order kinetic rate from the tablet's surface. Polymers such as HPMC, MCC, poly PLGA, and hydrophobic Gelucire are used in controlled-release SNEDDS formulations [9, 42, 43].

Mucus permeation SNEDDS

Mucosal surfaces in various body regions, including the nasal, ocular, lung, intestinal, and vaginal areas, are covered by an adhesive mucus layer that acts as a barrier. Formulating mucus-permeating formulations is a significant challenge. SNEDDS are considered superior mucus-permeating nanocarriers, as their hydrophobic nature allows them to traverse the mucus layer without becoming trapped. Smaller particle sizes, especially those below 50 nm, are more favourable for mucus penetration, as permeability depends on size. Studies have shown that SNEDDS with particle sizes less than 12 nm exhibit a significantly higher permeation of up to 70%, compared to 450 nm particles with 8% permeation. Modifying the charged surfaces of SNEDDS can further enhance penetration. Mucoadhesive polymers used in these formulations include HPMC, Cremophor RH 40, and Triacetin.

Bioactive SNEDDS

Bio macromolecules, such as lipids, proteins, and polysaccharides, are considered modern therapeutic agents due to their high specificity and low toxicity. However, their larger size and limited penetration capability pose challenges for incorporation into

formulations. SNEDDS have been shown to enhance the solubility, penetration, and bioavailability of these biomolecules. For example, insulin/chitosan-TGA SNEDDS formulations were developed for oral insulin delivery, resulting in increased drug release compared to marketed formulations. These formulations showed increased serum insulin levels in *in vivo* studies. Other mucus-permeating SNEDDS formulations enhanced mucus permeability, with the incorporation of insulin/Dimyristoyl phosphatidylglycerol (INS/DMPG) in SNEDDS preventing early burst release of insulin, offering a promising approach for oral insulin delivery [44, 45].

Self-double nano-emulsifying drug delivery systems (SDEDDS)

SDEDDS, consisting of hydrophilic surfactants with water-oil-water emulsions, are used for the delivery of peptide and protein drugs. SDEDDS protect peptides and drugs from enzymatic inactivation in the gastrointestinal tract (GIT) while improving their efficiency and reducing required doses [46].

Targeted SNEDDS

Targeted drug delivery aims to improve therapeutic efficacy and reduce toxicity. Nanoemulsions can remain in the body for extended periods, avoiding mononuclear phagocytes. Cationic droplets can be directed toward anionic membrane barriers, facilitating liver uptake for targeted delivery. PEGylation involves attaching polyethylene glycol (PEG) to nanodroplets, forming a barrier at the surface to prevent enzymatic degradation and enhance stability. Other polymers like HPMC and thiolated chitosan can be used to retain drugs in the GI tract, offering a targeted drug delivery approach.

Future scope

Recently, there has been a remarkable upswing in the field of research focused on Self-Nanoemulsifying Drug Delivery Systems (SNEDDS). Numerous studies have indicated that SNEDDS hold promise as an optimal drug delivery system. Researchers are actively exploring both conventional SNEDDS and Solid SNEDDS to uncover their potential in enhancing the oral absorption of pharmaceutical compounds. Here are some of the latest developments in the realm of SNEDDS. However, there is a critical need to assess the ph-catalyzed and solution-state degradation of drugs within SNEDDS. While the conversion of SNEDDS into a solid state can help reduce drug degradation, it may not completely eliminate this issue in many cases. Therefore, it is essential to identify strategies for modulating the microenvironment to improve the stability of ph-sensitive drugs. Notably, there is a growing interest in using inert adsorbents such as Neusilin and Zeopharm products to convert liquid SNEDDS into powders, which aids in the formulation of solid SNEDDS. However, achieving solid SNEDDS with suitable processing properties requires a high ratio of SNEDDS to solidifying excipients, which may not be practical for drugs with limited solubility in the oil phase. In this context, a hypothesis suggests that the number of solidifying excipients needed for transforming SNEDDS into solid dosage forms can be significantly reduced if SNEDDS are gelled. Colloidal silicon dioxide (Aerosil 200) is considered as a gelling agent for oil-based systems, serving the dual purpose of reducing the number of solidifying excipients required and slowing down drug release. Additionally, exploring the applications of SNEDDS in delivery routes other than oral administration is an area of growing interest. The successful commercialization of SNEDDS technology will depend on drug delivery scientists' ability to address these crucial aspects and overcome the challenges associated with SNEDDS, such as drug stability, solidification, and alternative delivery routes.

CONCLUSION

Owing to the recent advances in technology, there have been increments in the number of new chemical moieties discovered with each passing day. These novel drug molecules despite possessing enhanced targeting abilities with an appreciable potential, often lag behind when it comes to their efficient delivery since these molecules demonstrate poor absorption in the body. Lipid formulations have evolved as a promising solution for enhancing the bioavailability of a broad range of drug molecules possessing low aqueous solubility. Amongst the various lipid formulations employed to alter a drug's physicochemical properties, self-nano-emulsifying drug delivery systems (SNEDDS) offer appreciable advantages, including improved bioavailability, enhanced stability, higher drug loading capacity, potential for conversion to solid dosage forms (solid-SNEDDS), and facilitation of manufacturing with ease of scaling up. SNEDDS are particularly investigated for improving the bioavailability of BCS class II and IV drugs with low aqueous solubility. The self-nanoemulsifying drug delivery systems have varied characteristics thus making them one of the most ideal approaches employed for delivering active pharmaceutical ingredients. Due to their diverse and versatile characteristics, they have the potential to have a positive influence on many sectors, be it pharmaceuticals, biotechnology, cosmetics. Conventional approaches for enhancing bioavailability often fail to keep up when dealing with the increasing number of poorly soluble drug candidates. This study establishes the effectiveness of a self-nanoemulsifying system-based drug delivery approach, with a specific focus on solid SNEDDS.

ABBREVIATIONS

SNEDDS-Self-nano-emulsifying drug delivery systems

S-SNEDDS–Solid Self-nano-emulsifying drug delivery systems

SEEDS–Self-emulsifying drug delivery systems

SMEEDS-Self-micro-emulsifying drug delivery systems

PAMPA-Parallel artificial membrane permeability model

SDEDDS-Self-Double Nano Emulsifying Drug Delivery Systems (SDEDDS)

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CONFLICT OF INTERESTS

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