Available online on 15.08.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

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Review Article

Advances in Self-Nanoemulsifying Drug Delivery Systems: Mechanistic Insights and Formulation Strategies

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Article Info:

Article History:

Received 20 May 2025
Reviewed 29 June 2025
Accepted 23 July 2025
Published 15 August 2025

Cite this article as:

Ravi Smitha A, Mohanan J, Kuzhiyil Chalil A, Karakkunnummal FN, Advances in Self-Nanoemulsifying Drug Delivery Systems: Mechanistic Insights and Formulation Strategies, Journal of Drug Delivery and Therapeutics. 2025; 15(8):217-236 *DOI: http://dx.doi.org/10.22270/jddt.v15i8.7303*

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Abstract

Solubility enhancement is a significant challenge in oral drug delivery, particularly for Biopharmaceutical Classification System (BCS) Class II and IV drugs, which suffer from poor aqueous solubility. Lipid-based formulations, especially Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), have gained attention as effective solutions to this problem. SNEDDS are isotropic mixtures of oil, surfactant, and co-surfactant/co-solvent that spontaneously form nanoemulsions upon contact with gastrointestinal fluids. This review provides a detailed exploration of the formulation, characterization, and solidification techniques of SNEDDS, emphasizing the roles of lipids, surfactants, and co-surfactants in enhancing drug solubility and bioavailability. The article discusses various evaluation techniques for SNEDDS, including droplet size analysis, in vitro dissolution testing, lipolysis, and permeability studies, which are crucial for assessing their performance. Additionally, the review examines the solidification methods of SNEDDS, including adsorption, spray drying, hot melt extrusion, and lyophilization, which enhance formulation stability and scalability. The review also highlights recent innovations in solid SNEDDS (S-SNEDDS), emphasizing their potential in delivering biologics, personalizing therapy, and improving patient compliance. This article positions SNEDDS as a versatile and robust platform capable of significantly enhancing the oral bioavailability of poorly soluble drugs, making them an attractive and reliable solution for modern drug delivery challenges and therapeutic advancements.

Key words: SNEDDS (Self-nanoemulsifying drug delivery system), BCS (Biopharmaceutical Classification System), solubility enhancement, nanoemulsion, solidification techniques, bioavailability, self-emulsification, surfactants, co-surfactants, pseudo-ternary phase diagram.

Introduction

Solubility plays a vital role in ensuring that drugs achieve the necessary concentration in systemic circulation to produce the intended pharmacological effect[1]. In recent years, approximately 40–70% of newly developed therapeutic compounds have been classified under the Biopharmaceutical Classification System (BCS) Class II or IV, exhibiting poor aqueous solubility, which poses a significant challenge to their bioavailability[2]. Enhancing the solubility of such compounds remains a significant challenge in the drug development process, particularly in designing efficient oral drug delivery systems. For decades, the pharmaceutical industry has employed various solubility enhancement techniques to maximize the therapeutic potential of active pharmaceutical ingredients (APIs)[3]. Several conventional techniques have been utilized to enhance solubility, including salt formation, pH adjustment, permeation enhancers, surfactants, solid dispersions, cyclodextrin inclusion complexes, co-solvents, particle size reduction, and prodrug formation. However, lipid-based formulations have proven to be the most effective approach for enhancing the solubility of poorly soluble drugs[4].

The emergence of novel lipid-based excipients with proven regulatory acceptance and favorable safety profiles has significantly contributed to the advancement of lipid-based drug delivery systems, particularly for improving the oral bioavailability of poorly soluble drugs. Lipid formulations are especially beneficial for drugs that are inherently oil-like and or when conventional approaches such as granulation or encapsulation fail to enhance bioavailability[5]. These systems range from simple oil solutions to complex formulations comprising oils, co-solvents, surfactants, and co-surfactants, depending on the excipient selection and formulation design[6]. Lipid-based drug delivery systems (LBDDS) offer several significant advantages that make them highly suitable for modern pharmaceutical applications. These systems facilitate controlled and targeted drug release, enhancing therapeutic efficiency. They provide excellent pharmaceutical stability and support high drug-loading capacities compared to traditional carriers. LBDDSs are versatile in handling both lipophilic and hydrophilic drugs, broadening their application range. Additionally, they are composed of biodegradable and biocompatible materials, ensuring safety and compatibility within the body. The flexibility in choosing excipients and the

adaptability in formulation methods further add to their appeal. These systems generally possess a low-risk profile and enable the development of passive, non-invasive vesicular formulations that can be readily commercialized[7].

Among the various multifunctional nanocarriers developed as pharmaceutical drug delivery systems, lipid-based nanocarriers are highly regarded for their minimal in vivo toxicity. These nanocarriers include liposomes, niosomes, solid lipid nanoparticles (SLNs), lipid-polymer hybrid nanoparticles, nanoemulsions, lipid-based micelles, nanostructured lipid carriers (NLCs), and self-nanoemulsifying drug delivery systems (SNEDDS)[4]. Fig. 1 is the schematic representation of various lipid-based nanocarriers.

Among the various lipid-based drug delivery systems, self-nanoemulsifying drug delivery systems (SNEDDS) have garnered significant attention and are extensively studied for enhancing oral drug delivery. This paper offers a comprehensive overview of the development, characterization, evaluation, solidification, and future aspects of SNEDDSs.

SNEDDS

In general, "SNEDDSs are isotropic mixtures of the drug, oil, hydrophilic surfactants, and co-surfactant/co-solvent". They are anhydrous preconcentrates that spontaneously form oil-in-water nanoemulsions (particle size <100 nm) upon exposure to an aqueous phase and mild agitation from gastric motility[8,9]. SNEDDS can accommodate drug doses ranging from less than 25 mg to over 2 g[10].

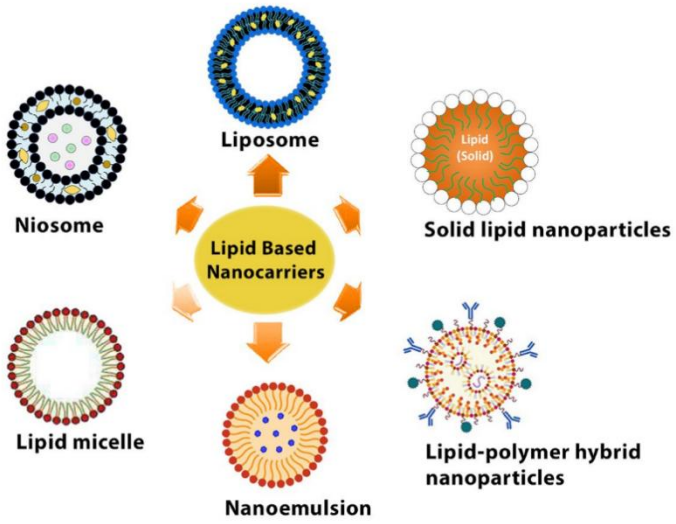

Figure 1: List of lipid-based nanocarriers for the delivery of active pharmaceutical ingredients

SNEDDS offer several advantages, including a rapid onset of action, straightforward preparation process, and easy scalability compared to other lipid-based drug delivery systems, making them highly suitable for industrial manufacturing[11]. They are also characterized by long-term stability, improved patient compliance, enhanced palatability, dose reduction, ease of formulation and scalability in synthesis, protection of sensitive drug substances, targeted delivery to specific absorption sites in the gastrointestinal tract, enhanced oral bioavailability allowing dose reduction, high drug loading capacity, thermodynamic stability that facilitates easy storage, improved drug dispersion through fine oil droplets that minimize gastrointestinal irritation, and a large interfacial area that enhances drug partitioning compared to conventional oily solutions[12]. The key features that contribute to enhanced oral bioavailability include the reduction of cytochrome P450 metabolism in intestinal enterocytes, increased lymphatic uptake via Peyer's patches, and reduced exposure to hepatic first-pass metabolism[2].

Mechanism of self-emulsification

Self-emulsification occurs when the increase in entropy that promotes dispersion exceeds the energy required to increase the interfacial area between the oil and aqueous phases. The free energy change (ΔG) involved in forming a conventional emulsion is directly proportional to the energy needed to generate a new interface, which is mathematically represented by the following equation:

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

Where:

ΔG = Free energy associated with emulsification,

N = Number of droplets,

r = Radius of droplets,

σ = Interfacial tension.

Over time, emulsions naturally tend to separate to minimize the interfacial area. Emulsifying agents help counteract this by forming a protective monolayer around the droplets, effectively reducing interfacial tension and preventing droplet coalescence. The

spontaneous formation of emulsions, or self-emulsification, is influenced by the specific combination of surfactant and co-surfactant. This combination often reduces the phase inversion temperature (PIT), thereby facilitating the formation of emulsions with minimal energy input[8,12].

SNEDDS action in the stomach

Following oral administration of SNEDDS, the digestive motility of the stomach generates the required agitation for self-emulsification, leading to the formation of a nanosized emulsion (20–200 nm) with an extensive interfacial surface area that enhances drug absorption[13]. This enhanced surface area improves drug solubilization and permeation by influencing transport properties and by bypassing the dissolution step[14]. These lipid-based nanocarriers can also enhance lymphatic uptake of highly lipophilic drugs (log P > 5 and lipid solubility > 50 mg/g), thereby reducing the first-pass effect and metabolism by cytochrome P450 (CYP450) enzymes[15]. In the fed state, bile salts facilitate the aggregation and entrapment of the drug within the lipophilic medium, thereby promoting its solubilization. Lipid-based formulations can indirectly facilitate this process, which will further aid in the absorption of SNEDDS[4]. Moreover, SNEDDS have been reported to enhance transcellular permeability by increasing the lipid fluidity of enterocyte membranes and inhibiting efflux pumps, thereby improving oral bioavailability[2]. Fig. 2 shows how intestinal drug transport occurs through lipid-based formulations.

SNEDDS components

a. Lipids

Lipids play a crucial role in SNEDDS, primarily influencing drug solubility, absorption, and formulation stability. The drug's solubility in the oil phase is a key factor in selecting suitable lipids, especially for oral delivery, where maintaining the drug in a solubilized form enhances bioavailability[16]. However, high solubility alone does not always translate to improved *in vivo* performance[17]. Also, Larsen et al. demonstrated that the highest drug absorption did not always correspond with the highest solubility, indicating that other formulation factors play a critical role[18]. For SNEDDS formulation, the oil phase must possess excellent drug solubility while promoting efficient nanoemulsion generation. Triglycerides are categorized by chain length into short (<C5), medium (C6–C12), and long (C12–C22) chains[8]. Medium-chain triglycerides (MCTs) offer good emulsification and promote absorption via the portal vein, and produce a small droplet size, but have limited lymphatic transport. Natural oils rich in MCTs, such as coconut and palm kernel oil, are preferred for their safety but are limited by poor drug-loading and emulsification properties. Therefore, modified MCTs (C8–C10; e.g., Capryol® 90, Captex® 300) and LCTs (>C10; e.g., Maisine®-35, Peceol®) are commonly used to enhance solubility. Long-chain lipids like oleic acid and castor oil can maintain drug solubility and reduce precipitation and also support lymphatic absorption by forming chylomicrons, bypassing hepatic metabolism, but long-chain triglycerides (LCTs) are more difficult to emulsify, leading to larger droplet size. A mixture of MCTs and LCTs is often used to balance these properties and improve pharmacokinetics[8,12,19].

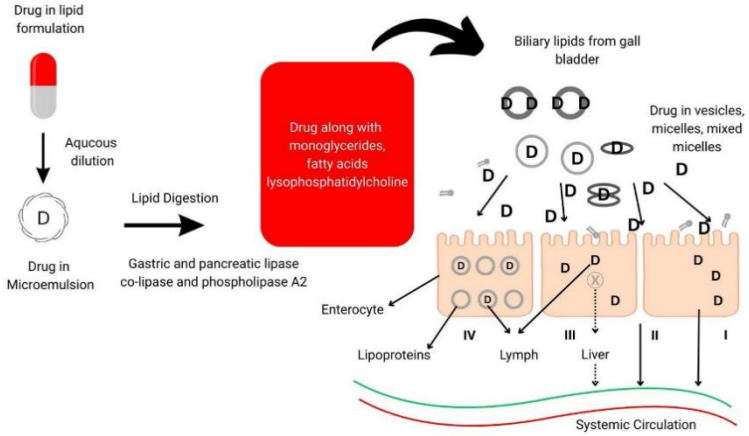

Figure 2: Schematic representation of transport of SNEDDS through the intestinal epithelium

b. Surfactants

Surfactants are essential components in SNEDDSs, primarily due to their amphiphilic nature, which enables them to enhance the solubility of lipophilic drugs in gastrointestinal fluids. These molecules possess both polar and non-polar segments, allowing them to reduce surface tension and stabilize the oil-water interface during nano-emulsion formation[8]. Surfactants are classified based on their ionization in aqueous solutions and hydrophilic-lipophilic balance (HLB). Based on their ionization in aqueous solutions, surfactants are anionic, cationic, non-ionic, or ampholytic. Based on HLB value, hydrophilic (HLB>10) or lipophilic (HLB<10). Among these, non-ionic surfactants with high hydrophilic-lipophilic balance (HLB) values (typically above 12) are most preferred due to their low toxicity and ability to produce stable nanoemulsions across a wide pH and ionic strength range[19]. In addition to their emulsifying function, certain non-ionic surfactants such as Tween® 80 and Cremophor® EL can enhance drug permeability by inhibiting efflux transporters like P-glycoprotein and increasing membrane fluidity[20]. The concentration of

surfactants plays a pivotal role in determining the particle size of nanoemulsions. While increasing their concentration generally reduces droplet size by further lowering interfacial tension, excessive levels may instead lead to larger droplets due to structural instability caused by water influx[21,22]. Moreover, despite their benefits, high surfactant levels may irritate the gastrointestinal mucosa. However, this adverse effect may be mitigated when the surfactants are integrated within emulsified systems. Thus, surfactants should be used in the lowest effective concentrations, and combinations of surfactants may be employed to achieve the desired formulation characteristics for safe and effective oral drug delivery[23]. Therefore, surfactant type, their emulsification efficiency, HLB value, and the maximum drug solubility offer are critical factors in formulation design.

c. Cosurfactants

These agents work synergistically with surfactants to improve drug solubility and enhance the dispersion of surfactants in the oil phase, thereby contributing to the overall homogeneity and stability of the nanoemulsion[24]. Cosurfactants or cosolvents play a vital role in the formulation of SNEDDS by enhancing various formulation attributes such as stability, drug loading capacity, emulsification efficiency, and droplet size[25]. Additionally, co-solvents help to reduce the local irritancy of surfactants and minimize dose variability by improving interfacial fluidity[26]. The weight ratio between surfactants and co-surfactants or co-solvents is a critical factor that influences the size distribution of droplets and the extent of the nanoemulsion region. However, it is essential to limit the use of cosolvents due to their polarity. Aqueous dispersion causes these solvents to migrate into the aqueous phase, potentially triggering drug precipitation. Moreover, volatile solvents such as alcohols can evaporate into capsule shells, further increasing the risk of precipitation. Therefore, careful selection and optimization of co-surfactants and co-solvents are necessary to achieve a stable and effective SNEDDS formulation[19]. Table 1 below shows some of the commonly used oils, surfactants, and cosurfactants in the development of SNEDDSs.

Table 1: Selected examples of oil, surfactant, cosurfactant for the preparation of SNEDDS along with the method of preparation

Oil **Surfactant** **Cosurfactant**	**Drug**	**Method used**	**Ref**
Virgin olive oil Tween 80 PEG 400	Meloxicam	Impregnation into solid carriers (mannitol and fumed silica) using a freeze-drying method	27
Cremophor RH 40 Lipoxol 300 PEG 400	Nimodipine (NIM)	Adsorption into chitosan EDTA microparticles	28
Labrafil M® 1944 CS Transcutol P® Cremophor® EL	Cyclosporin A	Entrapment into the matrix of polyvinylpyrrolidone K30 by fluid-bed coating to form pellets	29
Capryol 90 Cremophor RH 40 PEG 400/ 1,2-propanediol/ Transcutol HP	Myricetin	L-SNEDDS	30
Lauroglycol FCC Cremophor EL Transcutol HP	β-lactamase (Protein)	Fluorescent labelled SNEDDS	31
Kolliphor-EL Imwitor-308 Capmul MCM	Glibenclamide	S-SNEDDS by Adsorption into syloid Combined with a polymeric Amorphous System	32
Ethyl oleate Tween 80 Transcutol P	Zedoary essential oil	L-SNEDDS	33
Oleic acid Tween 80 Brij 30	Atorvastatin	L-SNEDDS	34

Capryol 90 Cremophor RH40 Transcutol HP	Olmesartan	Spray drying technique using Aerosil 200 as a solid carrier	35
Caproyl 90 Cremophor RH40/Cremophor EL Transcutol	Raloxifene hydrochloride (RLX)	L-SNEDDS (RLX was loaded in the alkalinized (A-SNEDDS) and nonalkalinized (NA-SNEDDS) systems	36
Capmul® MCM Gelucire® 48/16 propylene glycol	Quetiapine Fumarate (QTF)	Solidification via Hot-Melt Extrusion Technology using Soluplus® and Klucel™ EF as the solid carrier	37
Mentha oil Tween 80 PEG 200	Ornidazole	L-SNEDDS	38
Gelucire 44/14 Tween 80 PEG 400	Apigenin	L-SNEDDS	39
Capmul MCM Labrasol Tween 20	Ondansetron hydrochloride (ONH)	Solidification by adsorption on the porous carriers like Sylysia (350, 550, and 730) and Neusilin™ US2	40
Medium chain triglyceride and α-tocopherol in the ratio of (1:1) Kolliphor®EL Dimethylacetamide (DMA)	Triclabendazole (TBZ)	Solidification by liquisolid technique	3
Liquid paraffin Span 20 Capriole	Loratadin	Pelletization by extrusion-spheronization	41
Tea tree oil Tween 80 PEG 400	Cyproterone acetate (CPA)	L-SNEDDS	42
Labrafil Tween-80 Transcutol-HP	Indomethacin	Ultrafine SNEDDS	43
Capryol™ 90 Cremophore® EL Transcutol® HP	Clopidogrel (CLP)	Solidification by adsorbed onto Aeroperl® 300	44

Preparation of SNEDDS

a. Solubility studies

To optimize excipient selection for SNEDDS, the saturation solubility of the drug was evaluated in various oils, surfactants, and co-surfactants. To evaluate solubility, an excess amount of the drug was incorporated into 1–2 mL of each excipient and sealed within a vial or Eppendorf tube[3]. If needed, solid excipients were heated in a water bath at 45 °C to aid melting[11]. The mixtures were vortexed for approximately 2 minutes to ensure uniform dispersion and then incubated in a shaker maintained at 37 ± 2 °C for 48–72 hours to allow equilibrium to be established. After equilibration, the samples were centrifuged at speeds ranging from 4,000 to 10,000 rpm for 5–15 minutes, depending on the characteristics of the excipients. The clear supernatant was carefully withdrawn, filtered through a 0.45 µm syringe filter[45] or a millipore membrane filter[25], and appropriately diluted with suitable solvents. Quantitative determination was conducted using a validated UV spectrophotometric method or high-performance liquid chromatography (HPLC).

b. Screening of surfactants and cosurfactants

For the selection of surfactant, the emulsification efficiency of nonionic surfactants was assessed using percentage transmittance measurements and the number of flask inversions required to form a homogeneous emulsion. In this screening, surfactants were mixed in a 1:1 ratio with the selected oily phase, heated to 50°C for homogenization, and then diluted with water. The inversion count judged the ease of emulsification, while visual observation and UV-spectrophotometric evaluation were used to detect turbidity or phase separation[34,36,46]. Following surfactant selection, cosurfactants were screened based on their ability to enhance emulsification and their potential to

solubilize the drug. A surfactant and cosurfactant mixture, prepared in a 2:1 ratio, was combined with the oily phase in a 1:1 proportion, and its emulsification efficiency was evaluated using the same procedure[36,46]. The hydrophilic–lipophilic balance (HLB) also guided the selection process for formulating SNEDSS. The HLB value of surfactants and cosurfactants determines the balance between oil and water solubility, influencing emulsion formation. Surfactants with an HLB of 8–18 are ideal for oil-in-water emulsions, while water-in-oil emulsions are generally stabilized using surfactants with HLB values of 4–6. Selecting surfactant and co-surfactant with the right HLB minimizes trial and error, optimizing formulation[47].

c. Construction of pseudo-ternary phase diagram

To determine the optimal SNEDDS formulation, pseudo-ternary phase diagrams were constructed by titrating mixtures of oil, surfactant, and cosurfactant with water (aqueous titration method). Surfactant and co-surfactant were combined in various weight ratios (1:1, 1:2, 1:3, 3:1, and 2:1) to form the Smix. Smix was then mixed with oil in different ratios ranging from 1:9 to 9:1 (Oil: Smix). The oil-Smix mixtures were titrated with purified water dropwise while continuously vortexing after each addition at room temperature if needed. The process was carefully observed for turbidity, clarity, or phase separation. The weight of added water was recorded to determine the concentration of each component for constructing the phase diagram. Dispersions that appeared transparent or exhibited a slight bluish tint were identified as belonging to the nanoemulsion region.

Ashfaq et al. based on pitavastatin solubility studies, suitable oils (cinnamon oil, tea tree oil, and sesame oil), surfactant (Tween 80), and co-surfactant (PEG 400) were selected. Self-emulsifying formulations were prepared by varying concentrations of oil (20–60%), surfactant (30–80%), and co-surfactant (0–40%). To identify the self-emulsifying region, pseudo-ternary phase diagrams were constructed using CHEMIX® software in the absence of pitavastatin[48]. Zingale et al. for the formulation of resveratrol and melatonin SNEDDS intended for ocular delivery, the conventional aqueous titration technique was substituted by diluting the pre-SNEDDS mixture with simulated tear fluid (STF), consisting of NaCl, $NaHCO_3$, $CaCl_2 \cdot 2H_2O$, and KCl in distilled deionized water. The ternary phase diagram was developed by measuring the percentage transmittance using a UV–Visible spectrophotometer, with distilled water serving as the reference. Using Design of Experiment (DoE) software (Design Expert® 13.0), a simplex lattice design was employed for analysis[49]. Zhao et al. classified the ternary phase diagram into different regions based on emulsification efficiency. Formulations forming a clear, slightly bluish, or semi-transparent emulsion within 1 minute were labeled as Region A, representing the most efficient self-emulsifying formulations. Bright white emulsions (fine opaque or coarse emulsions) formed within 2 minutes were categorized under Region B, still meeting self-emulsification criteria. Dull, greyish-white emulsions with large oil droplets floating on the surface, taking longer than 2 minutes to form, were marked as Region C, indicating poor emulsification performance[50]. According to Xi et al. increasing co-surfactant concentration led to larger droplet sizes in nanoemulsion systems containing captex® 355, cremophor® EL, and transcutol® P due to interfacial film expansion by cosurfactant[51].Fig. 3 is a schematic representation of a pseudoternary phase diagram[52].

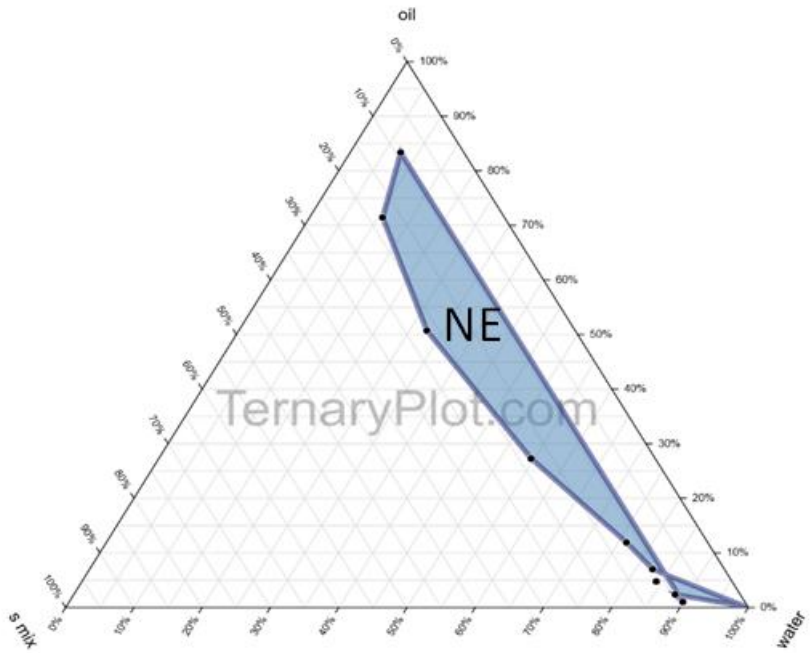

Figure 3: A pseudoternary phase diagram indicating nanoemulsion region. NE= Nanoemulsion region

Evaluation of SNEDDS

a. Droplet Size and Zeta Potential

Droplet size and zeta potential were simultaneously measured using a Zetasizer, offering insights into electrostatic stability, biodistribution, and intracellular uptake[53]. The formulations were dispersed in purified water at 37°C and gently mixed using a medium-sized rotator-vortex mixer. The sample was placed in a transparent plastic cuvette to minimize scattering error. Droplet size was determined by dynamic light scattering (DLS) at a scattering angle of 173°, while zeta potential measurements were conducted with mixed-mode measurement phase analysis light scattering (M3-PALS) technology at 37°C[54]. The droplet size (z-average) and zeta potential were expressed as mean ± standard deviation (n = 3), calculated based on signal intensity. The droplet size of emulsions derived from solid SNEDDS was specifically analysed using the Zetasizer Nano ZS90[55].

b. Self-emulsification time

Self-emulsification time refers to the duration required for an SNEDDS pre-concentrate to form a uniform nanoemulsion, becoming visually transparent. This was evaluated using different methods. Ashfaq et al. used USP dissolution Apparatus II (paddle type) operated at 100 rpm in a 900 mL phosphate buffer medium maintained at 37 ± 5°C to determine the self-emulsification time of pitvastatin SNEDDS. Two microliters of SNEDDS were introduced dropwise, and the time until complete disappearance was recorded[48]. Another method of Teaima et al. involved diluting the formulation 200-fold in a 0.3 M HCl buffer solution while continuously stirring at 100 rpm and 37 ± 0.5°C, monitoring the time taken for nanoemulsion formation[45]. Kumar et al. determined the self-emulsification time of nimodipine SNEDDS by dissolving 1 mL of each formulation into triple-distilled water and stirring at around 100 rpm with a magnetic stirrer. The emulsification process was visually observed, and the time required for complete dispersion was recorded[28].

c. Emulsification Study

USP Dissolution Apparatus II was employed to evaluate the emulsification efficiency of the SNEDDS formulation. The study involved adding 1 mL of the formulation to 100 mL - 500 mL of distilled water, maintained at 37°C, with a paddle rotation speed of 50 rpm -100 rpm [53,55]. The emulsification behavior was visually assessed using a standardized grading system as shown in Table 2[56].

d. Robustness to dilution

To simulate in vivo dilution effects, the formulations were diluted 10, 100, and or 1000 times using different media, including distilled water, 0.1 N HCl, and phosphate buffer (pH 4.5, 6.8,7.4). The diluted samples were stirred at 100 rpm and 37°C using a magnetic stirrer to ensure uniform mixing. The formulations were stored at ambient temperature for 24 hours, after which they were visually inspected for phase separation, indicating their stability upon dilution[35].

e. Cloud point measurement

The cloud point is the temperature at which a surfactant mixture undergoes phase separation, resulting in a turbid appearance due to emulsion destabilization[49].To determine this, selected formulations were diluted in distilled water at specific ratios (e.g., 1:100 or 1:250, v/v) and placed in a water bath with a controlled temperature increase. The temperature at which cloudiness appeared was recorded as the cloud point[46]. For spectrophotometric analysis, the reduction in sample transmittance from the initial zero point was measured at specific wavelengths to confirm turbidity[36]. Additionally, variations in Z-average particle size and polydispersity index (PDI) were assessed to verify nanoemulsion breakdown[49].

Table 2: Grading system for emulsification study

Grade A	Rapidly forming (within 1 min) nanoemulsion with a clear or bluish appearance.
Grade B	Rapidly forming (within 1–2 min) but slightly less clear nanoemulsion with a bluish-white appearance.
Grade C	Fine milky emulsion forming within 2 min.
Grade D	Dull, grayish-white emulsion with a slightly oily appearance, requiring more than 2 min to emulsify.
Grade E	Poor emulsification, characterized by large oil droplets on the surface, requires more than 3 min.

f. Percentage transmittance

Drug precipitation may occur in the gastrointestinal tract due to SNEDDS dilution. So, the percentage transmittance test was conducted to evaluate the clarity and stability of self-nanoemulsifying drug delivery systems (SNEDDS) upon dilution[28]. Nanoemulsions obtained from a 100-times dilution of SNEDDS in purified water were analysed for turbidity by measuring percent transmittance using a UV–Visible spectrophotometer, with purified water serving as the blank[11].

g. Drug loading efficiency

Loading efficiency represents the proportion of a drug successfully incorporated into a formulation relative to the total amount initially used. Kumar et al. determined the loading efficiency of nimodipine-SNEDDS by dispersing the SNEDDS formulation in methanol and vortexed using an orbital shaker for 10 minutes. The resulting solution was either directly analysed after appropriate dilution or, in the case of solid SNEDDS formulations, centrifuged, and the supernatant was then filtered through a 0.45 µm nylon Whatman filter paper

and analysed using a UV–VIS spectrophotometer at a specified wavelength[28]. The drug loading efficiency (%) was calculated using the following equation:

$$\text{Drug loading efficiency (\%)} = \frac{\text{Actual quantity of drug present in the known amount of formulation}}{\text{Initial drug load}} \times 100$$

h. Fourier Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was conducted to evaluate potential incompatibilities between the formulation components[57]. Various pure drug substances, excipients, and physical mixtures were analysed using an FTIR spectrometer. Solid Samples are dried under vacuum, finely mixed, and triturated with potassium bromide (KBr) at a 1:100 ratio. The mixture was compressed into pellets using a KBr press and placed in the sample holder for analysis. Liquid Samples are prepared as per the instrument's specifications before spectral recording[28]. Aziz et al. used a Thermo Fisher Scientific FTIR spectrometer within a spectral range of 650–4000 cm^{-1} to analyse molecular interactions and structural integrity. The spectrometer featured a diamond ATR interferometer, with an adjustable scanning speed of 0.1–4 cm/s and an IR beam diameter ranging from 2 to 11 mm. Spectra were recorded at a resolution of 4 cm^{-1}, with each sample scanned eight times, and the results were averaged to ensure accuracy[47].

i. Scanning electron microscopy (SEM)

SEM characterization provided detailed insights into the formulation topography (surface properties) and morphology (particle size, shape, and organization). The structural features of the pure drug and SNEDDS formulations were documented to evaluate their impact on formulation properties[47]. All imaging and data collection were conducted using a digital camera integrated with the SEM system. Samples were fixed on SEM stubs using double-sided carbon tape, sputter-coated with gold or platinum under vacuum, and imaged at different magnifications[29]. For nano-emulsions, 1 g of the formulation was diluted with 10 mL of phosphate buffer (pH 6.8) before mounting[34].

j. Transmission electron microscopy (TEM)

TEM was used to examine the morphological characteristics and confirm the globular size of SNEDDS formulations[58]. The samples were first diluted in distilled water, and a small drop of the diluted sample was placed onto a carbon-coated 400-mesh copper grid. Excess liquid was removed using filter paper, and the sample was stained using saturated uranyl acetate solution or 2% phosphotungstic acid to enhance contrast. The grid was then air-dried at room temperature before imaging[36].

k. Differential scanning calorimetry (DSC)

DSC was employed to assess the thermotropic characteristics of the sample[45].Various DSC instruments, such as the Pyris 6 DSC thermal analyzer, Shimadzu DSC-50, and Q200 modulated DSC, were utilized for this analysis. For performing DSC, samples were hermetically sealed in aluminum pans and subjected to analysis under a dry nitrogen atmosphere flowing at 20 mL/min. The scanning rate was maintained at 10 °C/min across different temperature ranges: 40–320 °C for Pyris 6 DSC, 0–230 °C for Shimadzu DSC-50, and 30–200 °C for Q200 DSC. An empty, hermetically sealed aluminum pan was utilized as the reference during analysis. Before heating, sample equilibration was carried out at 25 °C in the Q200 DSC system[45,59,60].

l. X-ray Diffraction (XRD) Analysis

XRD analysis was conducted to assess the crystallinity and polymorphic transitions of various formulations[45]. XRD patterns were recorded using different instruments, like XRD Aeries, Ultima IV X-ray Diffractometer, and D8 Advanced X-ray Diffractometer. Kumar et al. for the development of solid SNEDDS of nimodipine, the powdered sample was placed in a sample holder and continuously scanned from 10° to 50° at a rate of 2° per minute, with 0.02° 2θ increments using XRD Aeries. The scanning was performed at 25 °C, starting from 5° and ending at 50° (2θ), with the generator set at 45 kV[28]. Dash et al. used a D8 Advanced X-ray Diffractometer to perform X-ray powder scattering measurements on glipizide as well as on individual excipients of solid SNEDDS. The instrument utilized Cu Kα radiation produced at a voltage of 40 kV and a current of 40 mA[59].

m. Thermodynamic stability study

The thermodynamic stability of SNEDDS formulations was assessed through a series of stress tests, including freeze-thaw cycles, centrifugation, and heating-cooling cycles. Initially, the formulations were subjected to three freeze-thaw cycles, where they were frozen at -20°C for 24 hours and then thawed at 40°C for another 24 hours. After this, the samples were centrifuged at a suitable rpm for a suitable period to evaluate their stability as a single-phase isotropic system. Formulations that exhibited no phase separation, creaming, or cracking were further tested using three heating-cooling cycles, in which they were alternately incubated at 4°C and 45°C for 48 hours each. Only those formulations that remained stable under these conditions were selected for further studies[2,34,61].

n. *In vitro* Dissolution Study or *In vitro* Release Study

Both liquid and solid SNEDDS were evaluated using USP dissolution apparatus types I and II under controlled conditions. The dissolution media included 0.1 N HCl, phosphate buffer (pH 6.8), and water. Paddle speeds and temperature settings were optimized to simulate physiological conditions. Sample aliquots were periodically withdrawn, filtered, and analyzed to determine drug release rates. *In vitro* dissolution studies on L-SNEDDS were conducted using the hard gelatin capsule method, the dialysis bag method, and the dissolution cup method. Zhao et al. in the development of SNEDDS for oral delivery of zedoary essential oil, hard gelatin capsules containing SNEDDS formulations were subjected to dissolution testing in various media, including purified water, simulated gastric fluid (pH 1.2), and simulated intestinal fluid (pH 6.8). Samples were withdrawn at predetermined intervals, filtered, and analyzed using HPLC to determine the amount of drug release[50]. Aziz et al. employed the dialysis bag method to

evaluate the release profile of SNEDDS formulations in comparison with conventional drug suspensions. Dialysis membranes, pre-soaked in dissolution media (0.1 N HCl and PBS 6.8), were used to separate unbound drug molecules from the formulation. The study was conducted in a thermostatic water bath at 37°C with continuous stirring. Aliquots were collected at specified time points, filtered, and analyzed spectrophotometrically[47]. Elsheikh et al. used the dissolution cup method to study drug release from SNEDDS preconcentrates. A USP dissolution apparatus with paddle rotation was employed, using 0.1% Tween 80 in distilled water as the medium. Drug concentrations were monitored spectrophotometrically to assess release kinetics[36].

o. *In vitro* lipolysis

Falavigna et al. conducted the *in vitro* lipolysis study to evaluate the digestion and drug release behavior of SNEDDS formulations. Pre-weighed SNEDDS formulations were dispersed in high-throughput permeability (HTP) intestinal medium to achieve a final drug concentration, which is consistent with previous lipolysis studies. The dispersion was stirred at 37°C for 20 minutes before the addition of either 4 mL of pancreatic lipase solution for lipolysis assessment or 4 mL of HTP intestinal medium. Samples were collected at 0 and 30 minutes for drug distribution analysis. Lipolysis was inhibited by adding 5 µL of BBBA (benzyloxybenzyl barbituric acid) in 1 M methanol, followed by centrifugation to separate phases. The drug concentration in the aqueous phase was quantified using HPLC. pH monitoring was performed throughout the study, and droplet size before and after lipolysis was analyzed using Zetasizer.[62] Kazi et al. in the preparation of SNEDDS for Talinolol (TAL), an *in vitro* lipolysis study was performed by dispersing TAL-loaded formulations in digestion buffers under fed (pH 5.0) and fasted (pH 6.5) conditions, emulsified with SIF powder (taurocholate: lecithin in a 4:1 ratio). The lipolysis process was initiated by adding pancreatin extract, while the pH was maintained at 6.8 through a pH-stat titration unit. Fatty acids were quantified by titrating with 0.2 M NaOH. Post-digestion, samples were treated with 4-bromophenylboronic acid to inhibit further lipolysis, ultracentrifuged, and separated into aqueous and pellet phases. Drug content in each phase was analyzed via UHPLC (ultra-high performance liquid chromatography)[63]. Ashfaq et al. conducted an *in vitro* lipolysis study of pitvastatin SNEDDS, and the digestion products were separated into aqueous and pellet phases, and the drug content was analyzed using HPLC[48].

p. *In vitro* intestinal permeability and transport Studies

These studies provide insights into formulation permeability and absorption potential for oral drug delivery. Miryala et al. conducted rat intestinal permeability using modified literature methods for the study of SNEDDS for oral delivery of atorvastatin. Male albino rats (250–300 g) were euthanized with a pentobarbitone IV overdose. The isolated ileum was rinsed with Ringer's solution, and both ends were securely tied. 1 mg/mL of the test formulation was injected into the tissue and then placed in an organ bath. Permeability was evaluated using HPLC at set intervals. Cumulative drug absorption was compared with a marketed tablet.[34] According to *in vitro* transport studies of Zhang et al. MDCK cells (madin-darby canine kidney cells) were cultured on PET (polyethylene terephthalate) membrane transwells in a 24-well plate and incubated at 37°C, 5% CO_2. Trans-epithelial electrical resistance (TEER) was monitored until confluency (day 4–5). Before transport studies, monolayers were washed with HBSS (Hank's balanced salt solution). FITC-INS (Insulin labelled fluorescein) or FITC-IPC-SNEDDS (fluorescein isothiocyanate - Insulin phosphatidylcholine complex) was added to the donor compartment, and fluorescence spectroscopy determined apical-to-basolateral transport.[64] Falavigna et al. studied fenofibrate SNEDDS permeation using mucus-PVPA (mucus-phospholipid vesicle-based permeation assay). Samples were collected before and after lipolysis initiation. The barriers were placed in transwell acceptor wells containing DMSO-PBS (dimethyl sulfoxide-Phosphate-buffered saline). Samples were analyzed at different time intervals to determine drug permeation. Assessment of barrier integrity involved evaluating calcein diffusion and electrical resistance across the membrane. Fenofibrate and calcein concentrations were measured using spectrophotometry and fluorescence spectroscopy, respectively. The apparent permeability coefficient (Papp) was calculated to evaluate drug transport[62].

q. *Ex vivo* Permeation studies

Ex vivo permeability studies evaluate how well a drug molecule can permeate through a biological membrane, using live tissue detached from an animal body. Usually, these studies are conducted using adult male Wistar rats (200–250 g) that are housed under controlled conditions with unrestricted access to standard food and water. Before the study, they were fasted overnight but had free access to water. The rats were sacrificed via spinal dislocation, and the small intestine was excised by cutting between the duodenum's upper end and the ileum's lower end while removing the mesentery. The intestinal lumen was thoroughly cleaned using a blunt-ended syringe filled with Krebs-Ringer phosphate buffer (KRPB) solution. The intestine was then cut into different sections. The selected SNEDDS formulation was dispersed in 1 mL of KRPB, while a suspension of a marketed formulation (control) was prepared at the same drug concentration. Using a blunt needle, six ileal sacs were filled with SNEDDS formulations, while another six were filled with an equivalent amount of the control. The intestinal segments were securely tied at both ends with a thread and immersed in glass test tubes containing 10 mL of KRPB. The setup was maintained at 37°C in a shaking water bath at 100 rpm, and aerated using a laboratory aerator. At predetermined time intervals, samples were collected from the external medium, and the withdrawn volume was replenished with fresh Krebs-Ringer Phosphate Buffer (KRPB) to maintain consistent experimental conditions. The samples were analyzed using HPLC or UV spectroscopy. The permeability was assessed by plotting the cumulative amount of drug permeated through the

intestinal sac against time. The apparent permeability coefficient (Papp) was determined using the following formula:

$$\text{Papp (cm/sec)} = \frac{(dQ/dt)}{(A/Co)}$$

where dQ/dt represents the drug permeation rate across the intestinal membrane, A represents a cross-sectional area of the tissue, and C_0 is the initial drug concentration in the donor compartment at t_0[48,63].

r. *In vivo* Bioavailability study

Several *in vivo* studies have been conducted to evaluate the pharmacokinetic performance of SNEDDS in comparison to conventional formulations. Prasad et al. conducted bioavailability assessment of artemether and lumefantrine (AL)-loaded SNEDDS in Wistar rats (250–300 g), following ethical approval. The study compared AL SNEDDS with an AL suspension. Both formulations were administered orally, and blood samples were collected from the retro-orbital plexus at predefined intervals. After centrifugation, plasma samples were stored at −21°C for subsequent analysis[65]. Kale et al. performed a comparative bioavailability study of nimodipine (NM) SNEDDS. A crossover bioavailability study was conducted in rabbits (2.5 ± 0.3 kg) to compare SNEDDS with NM suspension, oily solution, and micellar solution. Each formulation was administered orally at 5 mg/kg, with a 7-day washout period between doses. Blood samples were collected from the peripheral ear vein, centrifuged to separate plasma or serum, and subsequently stored at −18°C to preserve sample integrity. Drug extraction from plasma was performed using a liquid-liquid extraction method, followed by HPLC analysis to determine drug concentration over time[66]. Baloch et al. evaluated the pharmacokinetic performance of chlorpromazine SNEDDS in Sprague-Dawley rats (200–250 g). The study compared three nanoformulations with a chlorpromazine suspension administered via oral gavage at 2 mg/kg. Blood samples were collected from the tail vein at predetermined time points, followed by centrifugation. Plasma drug extraction involved a combination of acetonitrile and methanol, and HPLC analysis was performed to determine plasma drug concentrations[2].

Solid SNEDDS

L-SNEDDS have recently gained significant attention for improving the solubility and bioavailability of poorly water-soluble drugs administered orally. Conventional liquid SNEDDS are typically encapsulated in soft gelatin capsules; however, long-term storage may present challenges such as drug precipitation at lower temperatures, leakage, excipient-capsule incompatibility, as well as handling and stability concerns[67]. To address these issues, converting L-SNEDDS into solid SNEDDS (S-SNEDDS) has emerged as an effective strategy, offering improved formulation stability. In addition to this, S-SNEDDS provide numerous benefits, including an increased surface area that enhances solubility and bioavailability, improved stability, robustness, ease of handling, and scalability. Additionally, they offer higher drug loading capacity, better flow properties, reduced drug precipitation, and cost-effective manufacturing[28]. Some of the commonly used excipients or carriers for solidification of SNEDDS, along with the method of solidification, are depicted in Table 3.

Table 3: Literature reviews of S-SNEDDS

Excipient used for solidification	**Drug**	**Solidification technique**	**Ref**
Hydrophobic carriers: Silicon dioxide, Magnesium stearate Hydrophilic carriers: polyvinyl alcohol (PVA), Sodium carboxymethyl cellulose (Na-CMC) , Hydroxypropyl-β-cyclodextrantrin (HP-β-CD)	Flurbiprofen	Spray-drying	68
Silicon dioxide	Docetaxel (DCT)	Spray-drying	69
Neusilin US2	Darunavir	Adsorption into carrier	70
Hydrophilic carriers Carbohydrates (lactose, mannitol) Complexing agents (maltodextrin, β-CD, dextrin) Polymers (soluble starch, HPMC)	Docosahexanoic acid (DHA)	Spay-drying	71
Galen IQ 981 (GIQ9), Galen IQ 721 (GIQ7), Aerosil 200 (AER-200), Hydroxy propyl methyl cellulose (HPMC), Sodium carboxy methyl cellulose (NaCMC), Syloid XDP 3514 (SXDP)	Curcumin	Adsorption into carriers	72

Fumed nano-sized silica, HPMC, Avicel, Plasdone XL , Mannitol	Finasteride (FSD)	Freeze drying	73
Polyvinyl caprolactam–polyvinyl acetate–polyethylene glycol graft copolymer (Soluplus®), Polyvinylpyrrolidonepolyvinyl acetate copolymer (Kollidon® VA 64), Polyvinylpyrrolidone (Kollidon®17 PF), Hydroxypropyl methylcellulose (Affinisol® HPMC 100 LV), Modified Eudragit® E copolymer (ModE) in different Mws (E-173 kDa, E-254 kDa, E-281 kDa, and E-305 kDa)	Celecoxib, Efavirenz, Fenofibrate	Hot melt extrusion	74
Silicon dioxide, Corn starch, Pregelatinized starch, Croscarmellose sodium, Microcrystalline cellulose	Sertraline	Extrusion-Spheronization	75
Adsorbents (Neusilin, Avicel and FujiSil), Binder (PVPK90), Disintegrant (Ac-Di-Sol)	Glimepiride	3-D Printing	76
Coffee husk	Talinolol	Adsorption into carriers	77

Solidification techniques

Several promising techniques that are already familiar within the field of industrial pharmacy can be applied for solidifying SNEDDS with certain modifications. Some of these techniques include spray drying, freeze-drying, and melt granulation. The choice of solidification method should be guided by factors such as the quantity of oily excipients present in the formulation, the physicochemical properties of the drug (e.g., solubility, thermal stability), and its compatibility with other formulation components[78]. Materials used for converting liquid SEDDS into solid forms must be inert and compatible. Moreover, they should support efficient drug loading, ensure an appropriate release profile, and exhibit suitable characteristics for downstream processing, such as good compressibility and flowability[79].

a. Filling in hard gelatin capsule

One of the most straightforward approaches to transform L-SNEDDS into S-SNEDDS is by directly filling them into gelatin capsules, as shown in the fig. 4. The volume of the formulation determines the capsule size, which makes this technique particularly suitable for low-dose, highly potent drugs.

Both liquid and semi-solid SNEDDS can be encapsulated, followed by sealing through banding, where a warm gelatin or HPMC (Hydroxy propyl methyl cellulose) band is rolled onto the capsule at the juncture between the body and cap lip[80] or micro-spray techniques, which use a small amount of a hydroalcoholic solution to create a seal between the capsule body and lid, followed by gentle heating to promote bonding[81]. It is a cost-effective and simple manufacturing process. But it is suitable only for small formulation volumes, and there is a chance of potential incompatibility between the formulation and capsule shell, or it may leak from the capsule shell[8].

b. Adsorption into solid carriers

"Adsorption is a surface phenomenon in which one or more components from a fluid, either gas or liquid, adhere to the external surface and internal surface of micropores of a solid porous material". This leads to the formation of a monolayer or multilayer on the surface. The fluid component being adsorbed is termed the adsorbate, while the solid porous material is referred to as the adsorbent[82]. It is a straightforward laboratory-scale process where L-SNEDDS is adsorbed onto solid carriers by manually blending them using a mortar and pestle, as depicted in Fig. 5. Physical adsorption in this method is governed by weak interactions such as van der Waals forces and electrostatic attractions[8]. The resulting powder is free-flowing, exhibits uniform drug content, and can be further processed into tablets or encapsulated in hard gelatin capsules[83].

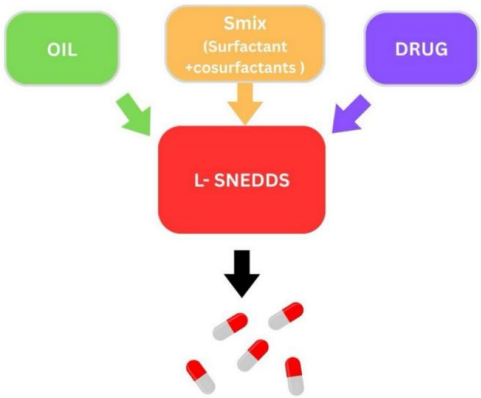

Figure 4: Filling of L-SNEDDS in gelatin capsule to form S-SNEDDS

Literature reports indicate that up to 50% (w/w) lipid loading does not negatively impact the flow properties, with some studies even documenting successful incorporation of up to 80%[78]. The choice of carrier material primarily depends on its porosity and specific surface area. In addition to this, the dissolution behaviour of the drug from the solidified SNEDDS may be influenced by potential interactions between the carrier material and either the drug or surfactants used[83–85]. Therefore, when developing S-SNEDDS via adsorption, factors such as particle size, specific surface area, type and quantity of adsorbent, and the physical state of the drug must be carefully optimized. Porous silica adsorbent powders have been successfully employed to transform lipid formulations into freely flowing powders, enhancing their practicality and stability. However, complete drug

release from SNEDDS was not achieved due to its entrapment within the deep pores of silica. To overcome this limitation, coating silica-based carriers with an immediate-release polymer to develop a co-processed excipient (CPE) has been proposed as an effective strategy to enhance overall SNEDDS release[60]. Daware et al. formulated a paediatric SNEDDS of triclabendazole using an adsorption technique for the treatment of fascioliasis[3]. Alothaid et al. used microcrystalline cellulose as a solid carrier for the formulation of supersaturated SNEDDS of albendazolum due to its favourable physicochemical properties, including surface area, porosity, hydrophobicity, and hydrophilicity[86]. Teaima et al. attempted to solidify L-SNEDDS of pioglitazone hydrochloride by adsorbing into four different adsorbents. On conducting in vitro release studies, S-SNEDDS formulated with syloid® 244FP (SYL) was preferred for further development in orodispersible tablet (ODT) formulation[45].

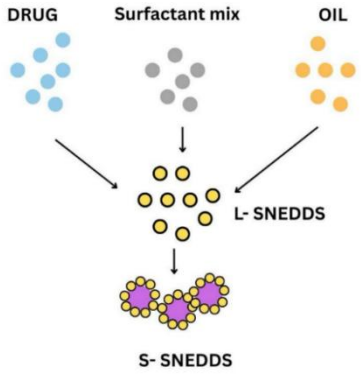

Figure 5: SNEDDS solidification by adsorption into solid carrier

c. Spray drying

Spray drying offers a straightforward, single-step approach to produce solid micro- or nanoparticles, including S-SNEDDS[87]. It is a technique used to convert a liquid or slurry into a dry powder by rapidly drying it with heated air. However, nitrogen may be employed when working with flammable solvents like ethanol or when the product is sensitive to oxygen[88]. In this process, the drug, lipids, surfactants, and solid carriers are first solubilized. This solution is then atomized into fine droplets, which are introduced into a drying chamber, allowing the volatile solvents to evaporate. This results in dry particle formation under controlled conditions. It is important to note that high drying temperatures can potentially compromise the stability of volatile excipients[8]. The process involves dissolving the solid carrier with the liquid formulation in a suitable solvent, followed by spraying into a heated chamber to evaporate the solvents, either water or organic, depending on the formulation. The fig. 6 shows a schematic representation of the spray drying technique. Precise regulation of temperature and airflow facilitates the formation of dried particles suitable for subsequent encapsulation or tablet compression. This method is compatible with a range of hydrophilic and hydrophobic carriers. The type of carrier used significantly influences the drug's release behaviour and absorption, as it affects the reconstituted droplet size and entrapment efficiency. Key spray drying parameters such as nozzle type, airflow rate, drying chamber temperature, and design must be tailored based on the desired powder characteristics and drying requirements[89]. Nasr et al. formulated S-SNEDDS via spray drying using aerosil 200 as a solid carrier. The SNEDDS and aerosil 200 were suspended in ethanol with continuous stirring until an isotropic mixture formed, then equilibrated at room temperature for 24 hours. The mixture was spray dried using a buchi mini spray dryer under controlled conditions like inlet temperature (60°C), outlet temperature (35°C), aspiration (85%), and suspension feeding rate (5 mL/min)[90]. Rajesh et al. optimized SNEDDS formulations were solidified via spray drying using different hydrophilic (PVA, Na-CMC, HPBCD) and hydrophobic carriers (PVA, Na-CMC, HPBCD). Ethanol was used to suspend hydrophobic carriers, while water served as the solvent for hydrophilic carriers. L-SNEDDS was added to each dispersion with continuous stirring at 100 rpm for homogenization. Spray drying was conducted using a 0.7 mm nozzle at a suitable pressure and flow rate. Inlet temperatures were 70°C (ethanolic dispersions) and 100°C (aqueous dispersions), with corresponding outlet temperatures of 35°C and 50°C, respectively[91].

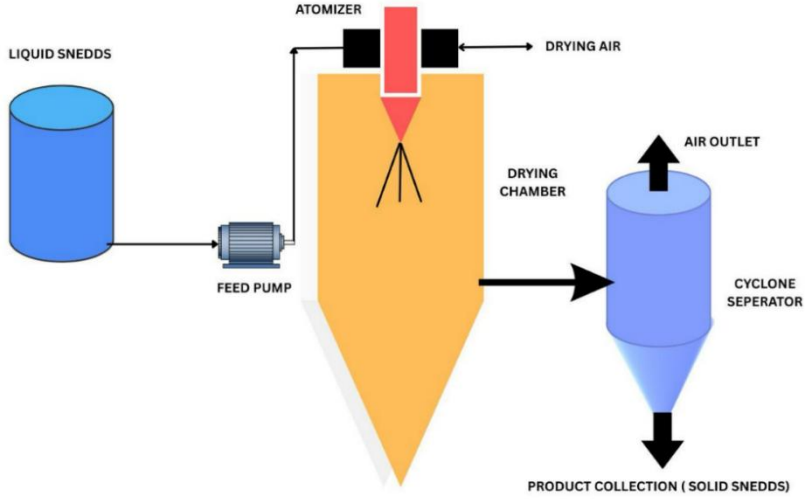

Fig. 6: Spray drying technique to form S-SNEDDS

d. Melt granulation

Melt granulation, or thermoplastic granulation, is a manufacturing technique used in pharmaceutics in which powder particles are agglomerated with the help of binders that can melt at comparatively lower temperatures (50–90 °C). It is a solvent-free, one-step technique widely utilized for preparing S-SNEDDS. This method eliminates the need for liquid addition and subsequent drying, offering a practical alternative to conventional granulation methods that rely on solvents. The final product is typically water-insoluble and non-swellable, making it safe for pharmaceutical applications[92]. Granule formation in melt granulation occurs through two primary mechanisms: immersion, where the primary particle is embedded into the molten binder surface, and dispersion, in which the molten binder uniformly coats the particle[93]. In the melt granulation process, binder melts to form liquid bridges between particles, leading to agglomeration and, under specific conditions, formation of spherical granules or pellets. The binder concentration generally ranges between 15–25%, depending on powder properties such as particle size and flowability[94].

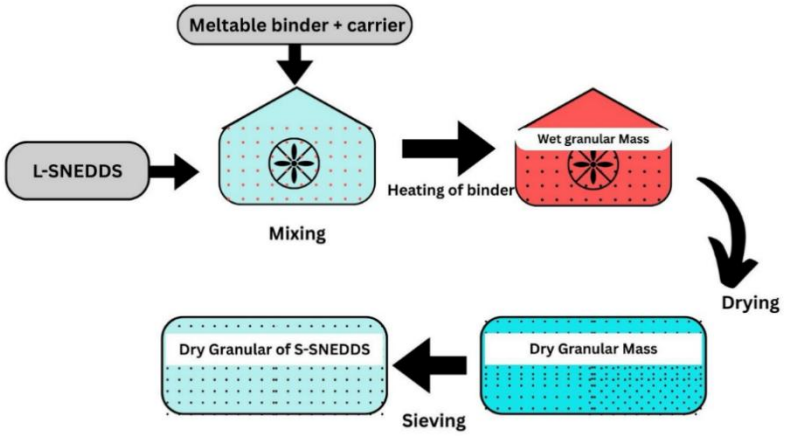

Figure 7: Solidification of SNEDDS by melt granulation

Commonly used adsorbents in this process include neutral solid carriers, such as silica and magnesium aluminometasilicate, as well as lipid-based carriers like gelucire and lecithin. This technique has been successfully employed to formulate immediate-release self-nanoemulsifying tablets. The resulting formulation showed enhanced stability without compromising the drug's rapid release profile[16]. Two primary approaches of melt granulation are a) In-situ or melt-in procedure, where solid binders melt during the process after being mixed with the drug and excipients. b) Spray-on or pump-on procedure, where molten binders, with or without the drug, are sprayed over heated powders to promote granulation[92]. Given its operational simplicity and exclusion of moisture and drying phases, melt granulation is particularly beneficial for formulating drugs that are sensitive to water or heat[95]. Schematic representation of melt granulation given in Fig. 7.

e. Hot melt extrusion

Extrusion is a manufacturing method used to produce materials with a consistent cross-sectional shape by forcing them through a die of the required design[96]. In this approach, the formulation is heated and pressurized, causing the carrier matrix to melt. The drug and polymer are blended due to the shear forces generated within the extruder barrel. As the material moves through the barrel, the heat and mechanical energy facilitate the incorporation of the drug into the molten polymer matrix. After processing, the molten mass exits through a die that imparts the final shape and dimensions to the extrudate[8]. Illustrated in Fig. 8. Uttreja et al. prepared S-SNEDDS using hot melt extrusion (HME). For which physical mixtures were fed into a HAAKE Minilab II extruder at 125°C and 50 rpm, with torque monitored throughout. The molten mass was extruded through a 2 mm spherical die, cooled, and made brittle using dry ice or liquid nitrogen. It was then milled, sieved (700 µm), and stored in sealed vials for analysis[37].

Schmied et al. for drug-loaded L-SNEDDS, various solubility-enhancing (co)polymers such as soluplus®, kollidon® VA 64, and affinisol® HPMC were blended with L-SNEDDS using a TURBULA® mixer. The mixtures were extruded using a co-rotating twin-screw extruder, cooled on a conveyor, and cut into granules. These were pulverized using a centrifugal mill (0.25 mm mesh) to obtain fine powders for further evaluation[74].

f. Extrusion-spheronization

Extrusion–spheronization is a widely used palletisation method in the pharmaceutical industry for producing solid dosage forms such as pellets, granules, and tablets[97]. In this technique, materials with plastic properties are forced through a die under controlled conditions of temperature and pressure to form uniform extrudates, which are then converted into spherical pellets through spheronization[89].

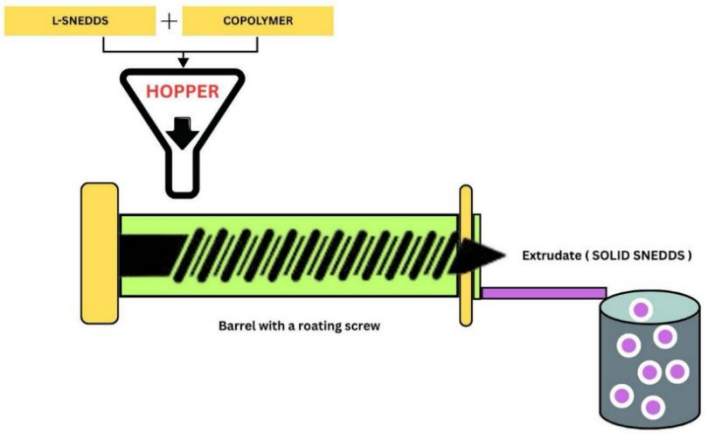

Figure 8: Hot melt extrusion technique for solidification of SNEDDS

This method is particularly effective for formulating self-nanoemulsifying pellets by mixing SNEDDS with carriers and wet massing agents. The extruded mass is shaped into spheroids with uniform particle size, good flow properties, and low friability, as depicted in Fig. 9. It also allows for high drug loading, with up to 42% of the dry pellet weight comprising SNEDDS[16]. Critical process steps include blending SNEDDS with adsorbents, wet massing, extrusion, spheronization, drying, and sieving. The final pellet characteristics depend on the SNEDDS-to-absorbent ratio, which influences extrusion force, disintegration time, particle size, and surface morphology. A higher proportion of absorbent can enhance SNEDDS incorporation, while reducing carrier quantity can improve drug loading. However, the method may require high energy due to processing temperatures and shear forces[89].

Abbaspour et al. prepared S-SNEDDS for loratadin by the extrusion-spheronization method, for which liquid SNEDDS was first adsorbed onto aerosil or a blend of avicel and lactose (for formulations without aerosil) using a kneader. The mixture was then mixed with MCC, lactose, and croscarmellose for 5 minutes. Distilled water was gradually added to form a consistent wet mass suitable for extrusion. The mass was extruded at 100 rpm through a 1 mm die and spheronized at 1000 rpm for 2 minutes. Pellets were dried at 40°C for 15 hours and stored in sealed bags[41]. According to Abdalla et al. SNEDDS content above 40% may lead to extrudate retention on the equipment surface. Additionally, insufficient adsorbent can lead to poor pellet hardness, low flowability, and agglomeration[98].

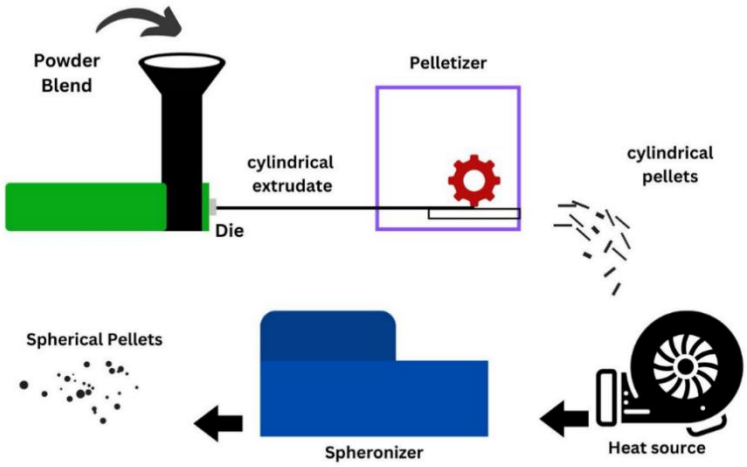

Figure 9: Extrusion-spheronization technique to form SNEDDS pellets

g. Freeze-drying

Lyophilization, also known as freeze-drying or cryodesiccation, is a dehydration method performed at low temperatures. Unlike conventional drying techniques that eliminate water via thermal evaporation, freeze-drying removes frozen water through sublimation under reduced pressure. This process helps preserve the structural integrity and quality of the product, making it especially suitable for thermo-sensitive substances[99]. The technique is widely used in pharmaceuticals, particularly for heat-sensitive drugs, as well as in food processing and biological preservation. The process comprises three primary stages: a) freezing, which solidifies the aqueous formulation; b) primary drying, where ice is removed through sublimation under vacuum; and c) secondary drying, which eliminates any residual, unfrozen moisture by desorption. Fig. 10. provides diagrammatic illustration of the freeze-drying process. The presence of excipients often aids in stabilizing the final product, especially in formulations where the initial material is in liquid form[8]. Kuncahyo et al. performed solidification of meloxicam SNEDDS by diluting it in a ratio of (1:10) by mixing it with mannitol (5 parts) and fumed silica (1 part). After overnight

freezing at −20°C, the mixture was freeze-dried at −60°C, 0.75 mBar for 24 h. Solid SNEDDS samples were placed in a desiccator for subsequent analysis[27]. Tashish et al. in adsorbent precoating by lyophilization, the precoating of adsorbent with hydrophilic polymers involved dissolving selected polymers (PVP-K30, PVP-K90, HPMC E3, or Soluplus) in aqueous solution at varying pH. The adsorbent was added to form a slurry, which was lyophilized at −60 °C for 48 h using Alpha 1-4 LD Plus. The resulting powder was ground manually and sieved through a 315 µm mesh for uniformity[100].

Figure 10: Preparation of SSNEDDS by freeze-drying

h. Supercritical fluid extraction method

Supercritical fluid extraction (SFE) employs a solvent maintained above its critical temperature and pressure to selectively isolate target compounds from solid or liquid substrates, taking advantage of the fluid's adjustable solvating properties[101]. Supercritical fluids (SCFs) offer a unique platform for the solidification of liquid formulations such as SNEDDS, primarily due to their tunable physicochemical properties. These methods enable the production of fine powders with narrow particle size distribution, often using lipids as coating agents or to form solid dispersions[102]. Carbon dioxide is the most commonly used SCF due to its low toxicity, nonflammability, cost-effectiveness, and recyclability. Other SCFs include nitrous oxide, ethylene, propane, and n-pentane. In this process, drugs and excipients are either dissolved in an organic solvent and then introduced into the SCF or directly processed in the SCF medium. As pressure and temperature decrease, solubility drops, causing the drug and lipid excipients to precipitate as coated microparticles or solid dispersions[16]. Schematic representation of the supercritical fluid extraction method is depicted in Fig. 11.

Key factors in this process include i) the solubility of the drug and excipients in the SCF, ii) the stability of the active substance under process conditions, and iii) environmental and energy concerns, especially regarding solvent evaporation. Notable SCF-based techniques are: Rapid Expansion of Supercritical Solutions (RESS), Gas Antisolvent Recrystallization (GAS), Precipitation with Compressed Antisolvent (PCA), Supercritical Fluid Impregnation, Solution Enhanced Dispersion by Supercritical Fluids (SEDS)[103].

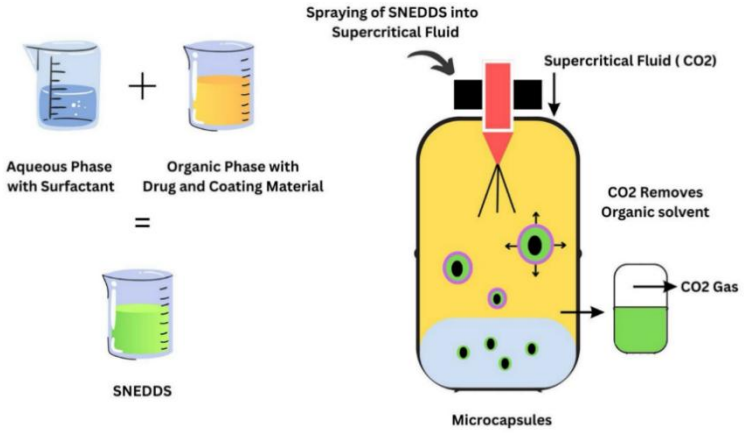

Figure 11: Solidification of L-SNEDDS by the Supercritical fluid method

SNEDDS in the market

Several commercial formulations based on SNEDDS have been successfully developed and launched to enhance the bioavailability of poorly water-soluble drugs. Some of the notable formulations are depicted in Table 4. These marketed products demonstrate the potential of SNEDDS to address formulation challenges associated with low oral bioavailability, variable absorption, and food-dependent pharmacokinetics. The success of these formulations underscores the industrial applicability and therapeutic advantages of SNEDDS in enhancing drug delivery efficiency.

Table 4: SNEDDS-based formulations in the market

Name	Drug and Excipients	Dosage form	Use	Ref
Fortovase®	Saquinavir	Soft gelatin capsules	Human immunodeficiency virus 11 (HIV11)	104
Norvir®	Ritonavir	Soft gelatin capsule	human immunodeficiency virus type 1 (HIV 1)	105
Spritam®	Levetiracetam	Mouth disintegrating tablet (3-D printed)	Epilepsy	106,107
Gengraf®	Cyclosporine	Soft gelatin capsule	immunosuppressant	108
Neoral®	Cyclosporine	Soft gelatin capsule	Immuno suppressant	109
Rapamune®	Sirolymus	Oral solution	Transplant rejection	110

Recent interests and future aspects

In recent years, nanomedicines have garnered significant attention as a drug delivery carrier. These nanoscale carriers offer several benefits, including biocompatibility, biodegradability, minimal toxicity, efficient drug delivery and targeting capabilities, as well as enhanced solubility, bioavailability, and therapeutic activity[111]. Recent advances in lipid and surfactant technologies, as well as integration with polymer science and targeting strategies, have expanded SNEDDS applications[23]. SNEDDS also show promise in delivering biomolecules like insulin and leuprorelin by enhancing permeability, reducing enzymatic degradation, and enabling lymphatic targeting. Surface modification further supports organ-specific drug delivery[4]. The future of S-SNEDDS is promising due to their versatility in forming tablets, pellets, and granules. Solidification improves formulation stability, patient compliance, and therapeutic efficacy while enabling controlled-release profiles. However, temperature-sensitive drugs pose a challenge in solidification, limiting their formulation. Overcoming this could facilitate the inclusion of biologics. Polymer-encapsulated SNEDDS can improve mucoadhesion, GIT retention, and protection against enzymatic degradation, offering sites for ligand attachment. The rise of personalized medicine may also see SNEDDS tailored to individual patient needs, enhancing treatment outcomes[112]. Further research is needed on suitable adsorbents for higher drug loading, particularly for complex drugs and biomolecules. Despite advances in *in vitro* testing, limited *in vivo* understanding hinders commercialization. Newer methods like HLB response surface methodology help optimize formulations more efficiently than traditional trial-and-error[4]. Finally, while nanomedicine-based SNEDDS show strong potential in targeted therapy, further clinical and toxicological studies in both animal and human models are essential to fully realize the potential and commercial application of nanomedicine-based drug delivery systems[111].

Conclusion

SNEDDS represents a highly effective lipid-based strategy to overcome solubility and bioavailability challenges in oral drug delivery. Their spontaneous emulsification, high drug loading, and ability to enhance lymphatic transport position them as a favourable choice for lipophilic drug delivery. Solidification techniques, such as adsorption onto porous carriers, spray drying, and hot melt extrusion, have further enhanced the applicability of SNEDDS by improving stability, handling, and patient acceptability. Despite the significant progress, challenges remain in solidifying temperature-sensitive drugs and scaling up production. Continued research focusing on novel excipients, targeted delivery, and in vivo performance will be critical to fully unlock the potential of SNEDDS in modern therapeutics and personalized medicine.

Conflict of Interest: The authors declare no potential conflict of interest concerning the contents, authorship, and/or publication of this article.

Author Contributions: All authors have equal contributions in the preparation of the manuscript and compilation.

Source of Support: Nil

Funding: The authors declared that this study has received no financial support.

Informed Consent Statement: Not applicable.

Data Availability Statement: The data supporting this paper are available in the cited references.

Ethical approval: Not applicable.

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