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REVIEW ARTICLE

From Liquid SNEDDS to Solid SNEDDS: A Comprehensive Review of Their Development and Pharmaceutical Applications

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Abstract

The liquid and solid formulations of self-nano-emulsifying drug delivery systems (SNEDDS) have garnered significant attention in the pharmaceutical field for their ability to enhance the solubility and absorption of hydrophobic drugs. While both liquid and solid SNEDDS result in improved bioavailability; portability, patient compliance, desired administration route, and ease of preparation are some factors that contribute to the decision-making of the final SNEDDS dosage form. This review provides a comprehensive analysis of SNEDDS formulations in the liquid and solid state, including production and performance factors that researchers ought to consider when developing their final dosage form. We investigate excipient characteristics, stability concerns, liquid-to-solid preparation methods and their challenges, and *in vivo* and *in vitro* comparisons of both dosage forms. Finally, we explore the potential of artificial intelligence in the design of SNEDDS formulations.

Keywords liquid SNEDDS · nano-emulsion · self-nano-emulsifying drug delivery system (SNEDDS) · solid SNEDDS

Introduction

Poor aqueous solubility is the primary limiting factor for drug design via the oral route. According to some estimates, 40% of marketed drugs and 90% of drug candidates respectively, are poorly water soluble (1). These drugs exhibit poor solubility in gastrointestinal (GI) fluids, and further low and variable oral bioavailability. While methods such as nanoparticles, solid dispersions/solutions, lipid-based systems, pH modification, salt formation and cyclodextrins, have been used to enhance drug solubility, self-nano-emulsifying drug delivery systems (SNEDDS) offer the combined benefit of nanotechnology and lipid-based drug delivery. SNEDDS comprise an isotropic mixture of oil, surfactant, and co-solvent, which spontaneously form an oil-in-water nano-emulsion once exposed to the aqueous media of the GI environment as shown in Figure 1 (2, 3). SNEDDS are characterized by their globule droplet size of ~10–200 nm, and often poor thermodynamic stability (4–8). SNEDDS can improve oral bioavailability, increase the dissolution rate, enhance drug absorption and overall therapeutic outcome (9). Furthermore, the activation of the lymphatic route caused by the presence of oils in the GI tract completely shields the absorbed drug from first-pass metabolism effects (10).

SNEDDS have potential applications in oral, parenteral, ophthalmic, intranasal, and cosmetic drug delivery (11–13). Particularly, they are often designed to target the oral route, and their dosage form is either liquid or solid. Both forms have a significant influence on the production process, behaviour and fate of the drug. Solid SNEDDS, characterized by their pre-dissolved state and subsequent conversion into nano-emulsions upon exposure to GI fluids, offer unique opportunities for controlled drug release and improved stability. On the other hand, liquid SNEDDS, already in a dispersed form, exhibit rapid emulsification properties, facilitating faster drug absorption and onset of action. Current trends in SNEDDS exploration reflect a growing interest in not only optimizing liquid SNEDDS but also transforming them into solid dosage forms to overcome limitations associated with liquid formulations such as stability concerns, leakage from

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capsules, and dosing inaccuracy. Solid SNEDDS can be developed either by converting liquid SNEDDS to solid SNEDDS or by preparing *de novo* formulations using solid/semi-solid excipients. Solidification techniques such as adsorption onto carriers, spray drying, freeze-drying, and melt extrusion have opened new avenues for developing more stable, patient-friendly, and commercially viable SNEDDS-based products.

While there have been several studies on SNEDDS formulations, there remains a lack of comparative analysis on the transition of SNEDDS from the liquid to the solid state (14–17). The review delves into the critical formulation parameters and design attributes for synthesizing both liquid and solid SNEDDS for improving drug solubility and bioavailability in orally administered dosage forms using various conversion techniques. Furthermore, we highlight benchtop to bedside challenges and advances of both liquid and solid SNEDDS formulations.

Liquid and Solid SNEDDS

SNEDDS are generally first formulated in liquid form, but can be converted to the solid dosage form for administration to the patient. The formation of SNEDDS is typically measured *in vitro* by adding the formulation into a dissolution apparatus or a beaker of medium at 37 °C under agitation, then recording the time until a transparent emulsion forms. Ideally, SNEDDS should self-emulsify under slight agitation within 3 minutes (17, 18). A timeframe that exceeds this suggests poor self-emulsification, risk of incomplete dispersion or larger droplet size. Solidification of SNEDDS can be performed to improve the stability of liquid SNEDDS or to offer alternative dosage forms. However, formulating SNEDDS directly in a solid or semi-solid state without first preparing a liquid intermediate is still possible. This method involves replacing liquid oils with solid/semi-solid lipids and pre-blending them with solid surfactants (19–22). While both solid and liquid SNEDDS can overcome bioavailability concerns, there are fundamental aspects to consider during preparation and final formulation.

Choice of Excipients

The primary constituents of SNEDDS are oil, surfactant, and co-solvent. The choice and concentration of each of these excipients can dictate the performance of the delivery system as a loading system for the drug, as well as the stability of the formulation. During SNEDDS formulation, the right concentration and combination of excipients are carefully selected to ensure that the end result is an emulsion size below 200 nm. The oil/surfactant/co-solvent ratio is usually 10–70%/30–75%/0–25% to obtain the self-emulsifying effect (23, 24). The selection of oil is primarily based on the drug's solubility in the oil, and the concentration of the oil also informs the degree of emulsification. Studies have noted that lower contents of oil (10–20% w/w) could produce rapid emulsification and small droplet size (25, 26). However, oils could also be selected because of their high degree of emulsification despite poor drug solubility in the oil (27). Oils with long-chain hydrocarbons (> 10 carbons), such as fixed oils (e.g. sesame oil, peanut oil and olive oil) are challenging to form nano-emulsions; however, their resulting droplet size is much smaller than oils with medium (~8–10 carbons) or short-chain length oils (< 8 carbons) (28, 29). Oils with medium-chain and short-chain lengths, such as capric triglycerides and triacetin, respectively, easily form nano-emulsions compared to long-chain triglycerides, but tend to have lower solubilizing capacity towards hydrophobic drugs (28, 29).

Examples of some oils used in SNEDDS formulations include essential oils such as lavender oil, avocado oil, and

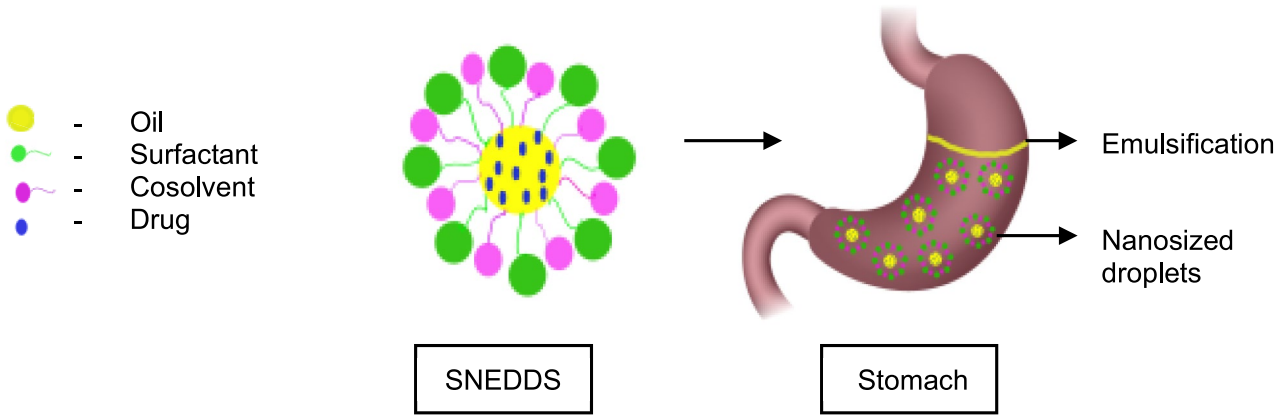

Fig. 1 SNEDDS emulsify to nano-sized droplets once exposed to gastric fluid

lemon oil; fatty acids such as oleic acid, fish oil, castor oil, and linolenic acid; and synthetic oils such as Maisine® CC and the Labrafil family of polyglycolysed oils (30, 31). Essential oils are a safe excipient choice and their antioxidant property, antibacterial activity and ability to enhance drug penetration in the small intestines make them an ideal candidate for SNEDDS delivery (32–35). On the other hand, synthetic oils have gained increasing attention in SNEDDS formulation because of their rapid ability to solubilise pharmaceutical drugs (36). A higher drug solubility in the oil phase will decrease the concentration of surfactant and co-solvent needed for emulsification of drug-loaded oil droplets. Moreover, some oils such as oleic acid can function as surfactants. Above the pK_a, oleic acid has ionic surfactant properties, while below the pK_a, oleic acid is protonated, and its properties change to that of oil (37). This property can be advantageous in providing solubility and nano-emulsion.

A surfactant's high hydrophilicity is important for the instantaneous formation of nano-emulsion droplets, but it is often challenging for a single surfactant to produce transient negative interfacial tension (38–40). Therefore, co-surfactants/co-solvents are employed and selected based on their ability to maximize the nano-emulsion area with the selected surfactant. Surfactants such as polysorbate 20/80, Labrasol, Cremophor EL, and medium to short chain length co-surfactants/co-solvents, such as PEG 200/400, Transcutol® HP and ethanol have been used in SNEDDS formulation (26, 41, 42). A more detailed list of examples of SNEDDS excipients is presented in Figure 2. Some studies have revealed that surfactants with branched alkyl structures such as Cremophor® RH 40 and Cremophor® EL are better for self-nano-emulsification (43, 44). An increase in the surfactant concentration can result in smaller globule sizes; this may be because surfactant molecules tend to absorb the oil-water interface, where they can stabilize the oil globules and prevent coalescence (20, 45, 46). However, excessively increasing the surfactant concentration increases the viscosity of the liquid SNEDDS, which limits the pourability of liquid SNEDDS into soft gelatin capsules, increases droplet size and reduces emulsification rate.

Non-ionic surfactants are typically preferred for SNEDDS formulation because of their lower toxicity and maintained nano-emulsion stability over pH changes in the GI tract (47). According to the value of the lipophilic-hydrophilic equilibrium (HLB), surfactants can be categorized as lipophilic (HLB < 10) or hydrophilic (HLB > 10) surfactants (48). Lipophilic surfactants with HLB < 10 preferentially stabilize water-in-oil emulsions, whereas SNEDDS for oral delivery require oil-in-water nano-emulsions (since the GI tract is an aqueous environment) (44, 49). Therefore, surfactants with HLB above 10 are used to produce more stable oil-in-water nano-emulsions. A drawback of the SNEDDS excipient combination is its poor palatability and irritating smell, which can be unattractive to some patients.

When considering solid SNEDDS as the end goal, initial excipients used should be carefully selected based on the conversion method and specific desired solid dosage form. Non-ionic, amphiphilic surfactants are preferred for the formulation of solid SNEDDS as they do not cause significant charge interactions with excipients (especially with adsorbers), making them ideal for solid-state stabilization (50). Surfactant concentration can also be reduced in solid SNEDDS, which offers less toxicity for long-term use than the liquid counterpart. Additionally, conversion to solid SNEDDS can contribute to masking the irritating smell often perceived in liquid SNEDDS. The conversion method of SNEDDS usually involves the incorporation of porous carriers such as crosslinked porous silicon dioxide, magnesium trisilicate, magnesium aluminometasilicate, talcum, crosslinked sodium carboxymethyl cellulose, cross-linked polymethyl methacrylate, and crospovidone (7, 51–55). According to our literature search, adsorbents form the simplest and most extensively used method for liquid-to-solid SNEDDS conversion. However, a high concentration of adsorbents may be needed to obtain excellent flowability of solid SNEDDS. This increases the volume dose and may affect patient acceptability and compliance. Additionally, adsorbents increase the adhesion capacity of solid SNEDDS particles, which may lead to poor disintegration (26). To combat these challenges, solid SNEDDS are often filled into hard gelatin capsules and more recently, one study reported the formulation of SNEDDS into orally disintegrating tablets (26, 56, 57). Solid carriers for SNEDDS are selected based on their ability to absorb and retain a high amount of liquid SNEDDS without compromising flowability. Some commonly used carriers and their specific properties for solid SNEDDS conversion are listed in Table I.

In *de novo* SNEDDS designed without a liquid intermediate, drug, solid lipids, and surfactants are melted and processed into granules or extrudates that self-nano-emulsify upon dispersion. Instead of using porous carriers, solid surfactants like sodium lauryl sulfate or poloxamers can form the base, eliminating the need for a prior liquid formulation. Amphiphilic polymers such as hydroxypropyl methylcellulose acetate succinate, (HPMC-AS), Soluplus® and copovidone, combined with solid/semi-solid lipids create *de novo* solid matrices that have both solubilization and self-emulsifying capacity (37, 69–71). The lipid and surfactant selection in *de novo* SNEDDS is usually based on their solid properties and melting points. The melting point of the chosen excipients is critical: it should be high enough to maintain formulation stability at room temperature, but low enough to allow processing methods such as melt granulation or hot melt extrusion without degrading the drug. Gelucires and poloxamers are the most common semi-solid

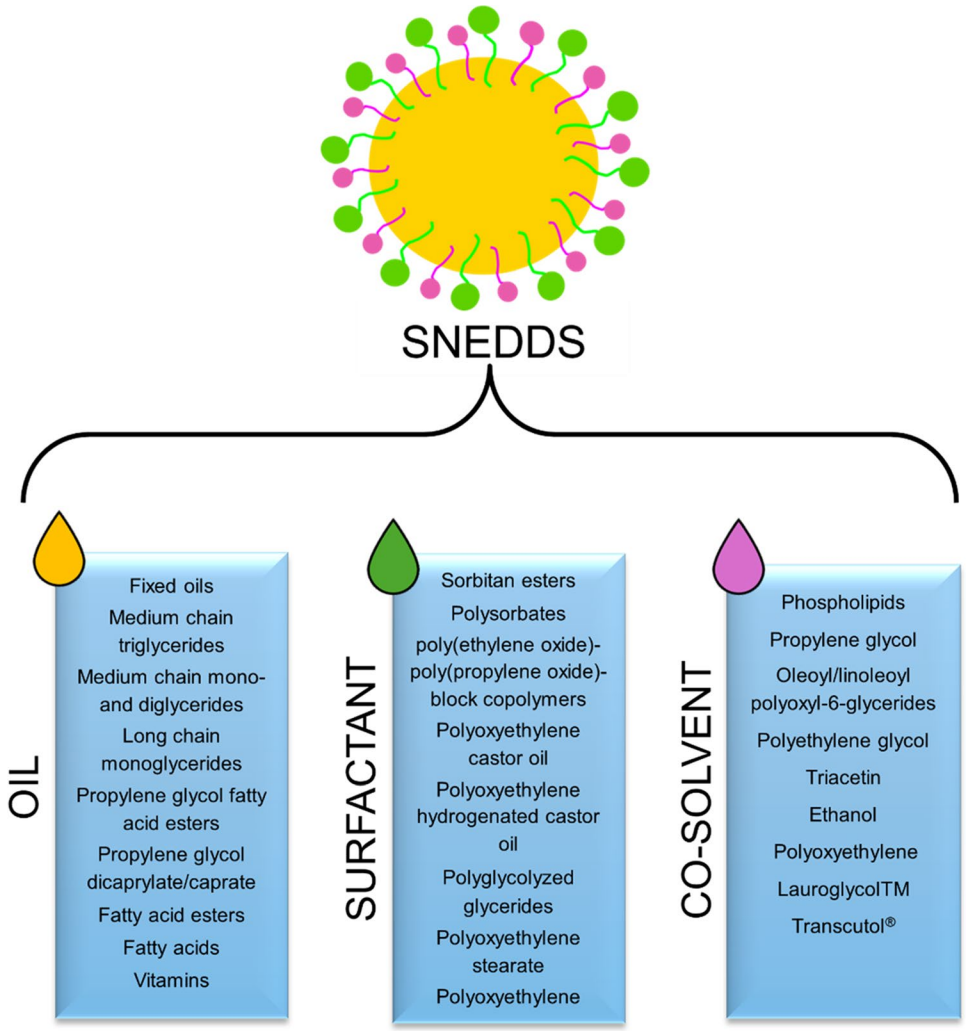

Fig. 2 Examples of SNEDDS excipients

surfactant bases due to their amphiphilic character and low melting points that enable processing. Solid lipids such as Compritol, Precirol, and stearic acid contribute to stability and allow solid dosage development, though they have lower solubilizing capacity (72, 73).

Preparation Method and Conversion Challenges

Liquid SNEDDSs are designed using a long "trial and error approach", ternary phase diagrams, or Box–Behnken design, where various types and concentrations of oils, surfactants and co-solvents are investigated for the fastest self-emulsifying quality, high drug solubilization and good initial stability. Furthermore, the route of SNEDDS solidification requires complex equipment and extra characterisation steps - a time-consuming and costly approach that may limit its exploration. The liquid-to-solid conversion method must be carefully selected to ensure its compatibility with the excipients and drug. This conversion to solid SNEDDS is usually performed using techniques such as spray drying, freeze drying, hot melt extrusion, melt granulation and/or adsorption into solid carriers.

Adsorption of SNEDDS is performed by wet granulation of the SNEDDS into the porous carrier to create granules or pellets. The rate of carrier adsorption is dependent on the porosity of the carrier. Factors such as particle size, and surface area of the porous carrier may influence drug release from the solid SNEDDS (74). Carriers with a larger pore size (> 50 nm) can allow enough space for SNEDDS entrapment and emulsification in contrast to carriers with smaller mesoporous interiors, which increase the interaction of SNEDDS to the outer surface of the carrier, leading to poor dissolution and drug precipitation (74).

When considering spray drying as the preferred conversion method to solid SNEDDS, it is preferable to strive for an oil/surfactant/co-solvent blend with a low viscosity in order to obtain rapid evaporation and drying with finer, uniform droplet sizes. Additionally, spray drying of oils often involves very high temperatures, which may degrade or denature thermally sensitive drugs and proteins. Therefore,

Table I Examples of Carriers Used in Solid SNEDDS and Their Distinct Properties

Carrier	Characteristics	Pore size (nm)	Particle size (nm)	Surface area (m^2/g)	References
Silicon Dioxide	Excellent adsorbent. Usually used to obtain small-sized SNEDDS.	~ 2–10	~ 200	1.6	(58)
Sylysia® 350		21	1800	300	(59)
Sylysia® 320		21	1600	300	
Neusilin® FL2		–	2000–8000	150	
Neusilin® UFL2		–	2000–8000	300	
Magnesium Aluminium silicate	Increases drug loading	~ 2.58	~ 30	124.25	(60, 61)
Microcrystalline Cellulose	Excellent compressibility for pallet formulation of SNEDDS.	Non-porous	~ 50000	~ 1.29	(62)
Lactose	Used as diluents with good flow characteristics. Best for lyophilization. Small pore	~ 0.075	~ 1.18	~ 35	(63)
Mannitol	Masks poor palatability of SNEDDS. Good diluent	~ 3.7	~ 15000	~ 1	(64, 65)
Calcium carbonate	Chemically stable Prevents moisture absorption.	30–50	5–15	40–80	(58, 66)
Starch	Biodegradable and GRAS-approved	2–200	0–25000	~ 0.8	(58, 67)
Talcum	Improves flow properties of SNEDDS powder	34.28	~ 27000	~ 2.51	(68)

a good compatibility assessment of the active pharmaceutical ingredient, as well as adequate atomization parameters, must be confirmed before spray drying.

Hot melt extrusion is a multi-component system which involves a solid carrier and liquid SNEDDS. Due to its complexity, the process is not frequently preferred in the design of solid SNEDDS. Hot melt extrusion requires a careful simultaneous mixing of both liquid SNEDDS and solid carrier to maintain the correct mixing ratio of the individual components and their uniform distribution in the final solid SNEDDS (31). Extrusion temperatures must be above the glass transition temperature (T_g) of the solid carrier, else they risk decomposition of the other excipients and active ingredients. Additionally, the high thermal energy and mechanical forces used during hot melt extrusion may disrupt the nano-emulsion structure, leading to phase separation or droplet coalescence, which can impact drug solubility and absorption. Therefore, several preliminary tests are necessary to determine the ranges of extruder operating conditions and the elemental composition of the formulation to ensure a successful extrusion process as well as the ability of the extrudates to form a suitable emulsion after fast emulsification process in an acidic medium (20). Torque values exceeding > 200 N.cm are associated with a high melt viscosity which could clog the extruder die and increase extrusion temperatures (31). It is therefore critical to develop liquid SNEDDS with low viscosity if hot melt/spray drying is the preferred method of solidification.

Granulation, particularly wet and melt granulation, has been explored as a strategy to transform liquid SNEDDS into solid dosage forms or to design *de novo* solid SNEDDS (75). Like in the case of extrusion, a primary limitation is the requirement for high energy input and elevated processing temperatures, which restricts its use with heat-sensitive drugs and excipients. Additionally, the viscosity and thermoplastic behaviour of the SNEDDS formulation play a crucial role in determining granule size, nucleation, and consolidation (76, 77). High viscosity can hinder the dripping and dispersion of the binder liquid, whereas binders with low melting points risk softening and instability during handling and storage. Another challenge lies in the physical properties of the granules. Depending on the equipment used, fluid-bed granulation often produces porous, irregular granules with poor flowability, while high-shear granulation yields denser, more spherical granules but can also result in longer disintegration times due to oily bridges within the matrix (9, 78, 79). Both scenarios affect subsequent downstream processes such as tabletting and capsule filling, where flowability and compressibility are critical. Moreover, achieving a high liquid load to maximize drug incorporation frequently compromises flow properties, leading to sticky granules with limited industrial scalability (79).

Lyophilization/freeze-drying of liquid SNEDDS has been scarcely explored in solid SNEDDS development, likely because oils have a low freezing point and are unable to form a solid matrix. However, the addition of adsorbents enables the lyophilization process of SNEDDS. The method constitutes freezing the adsorbent-based solid SNEDDS and then sublimating them at lower temperatures and pressures. Carriers such as mannitol and lactulose are suitable for

SNEDDS lyophilization due to their cryoprotectant nature. Some interesting methods have been used to develop lyophilized SNEDDS. In one study, the researchers diluted the liquid SNEDD 10 times and added the respective carriers- mannitol and silica (65). Thereafter, the SNEDDS was lyophilized to form solid SNEDDS. Other studies have taken the route of first lyophilizing a slurry which consists of adsorbent and polymer, then loading this into liquid SNEDDS which subsequently solidifies because of the presence of the adsorbent (7, 80). These lyophilized formulations typically produce very stable solid SNEDDS (81). As lyophilization is a suitable option for thermolabile compounds, solid SNEDDS should be explored using the approach. Figure 3 summarises the conversion methods used in SNEDDS formulations and some common dosage forms obtained from each liquid/solid state.

The term 'droplet size' is often used interchangeably with 'particle size' when considering solid SNEDDS (38, 82, 83). A plausible explanation would be that the SNEDDS system (whether liquid or solid) forms nano-sized droplets upon dispersion in an aqueous medium, and these droplets are the primary 'particles' that influence the formulation's properties. Aside from literature which narrates the impact of solid adsorbents on SNEDDS properties, there remains an absence of comparative studies that highlight the effect of different solidification techniques on the properties of solid SNEDDS. It is therefore difficult to ascertain which method produces the smallest droplet sizes and polydispersity index (PDI), improved solubility and dissolution of solid SNEDDS formulations. However, when considering the droplet sizes, there may be a slight increase in droplet size after conversion to solid SNEDDS, although this varies in the literature (82). While the individual droplets within the solid nano-emulsion may not be the same size as the original liquid SNEDDS, the self-nanoemulsifying properties and the drug's dispersion within the GI system are often maintained. Table II presents some examples of solid SNEDDS that have been formulated with different solid carriers and conversion methods.

Stability Concerns

SNEDDS stability in the liquid and solid state is critical to ensure consistent performance. It is possible to design stable liquid SNEDDS— in fact, several studies have reported good physical and chemical stability of liquid SNEDDS formulations over several months (84–88). The commonality in these studies is the absence or low concentration of co-solvents, small droplet sizes and PDI values below 0.3, which reduces the risk of creaming, phase separation, coalescence, and Ostwald ripening— factors that can affect the physical stability of the liquid SNEDDS over time (14, 17, 89). Additionally, liquid SNEDDS constituents are prone to degradation reactions such as hydrolysis, oxidation, and photolysis, and therefore exposure to oxygen, light, moisture and elevated temperatures can accelerate the degradation of liquid SNEDDS (90). Oxygen-impermeable, light-resistant packaging, such as amber glasses and aluminium blister packs, respectively, is used to protect liquid SNEDDS against oxidation. Singh and colleagues compared the oxidative stability of solid and liquid docosahexanoic acid oil-based SNEDDS (91). Their findings revealed that although both dosage forms produced peroxide over time, the peroxide content was double in liquid SNEDDS. Another study also concluded that solid SNEDDS degrade the active pharmaceutical drug at a slower pace than liquid SNEDDS (92). In liquid SNEDDS encapsulated by gelatin, stability against environmental factors is enhanced; however, precipitation of the drug during manufacturing or storage, incompatibility with the capsule shell, leakage and rancidity are still factors of concern. The oil concentration plays an important role in the stability of liquid SNEDDS; the lesser the oil content, the more stable the formulation

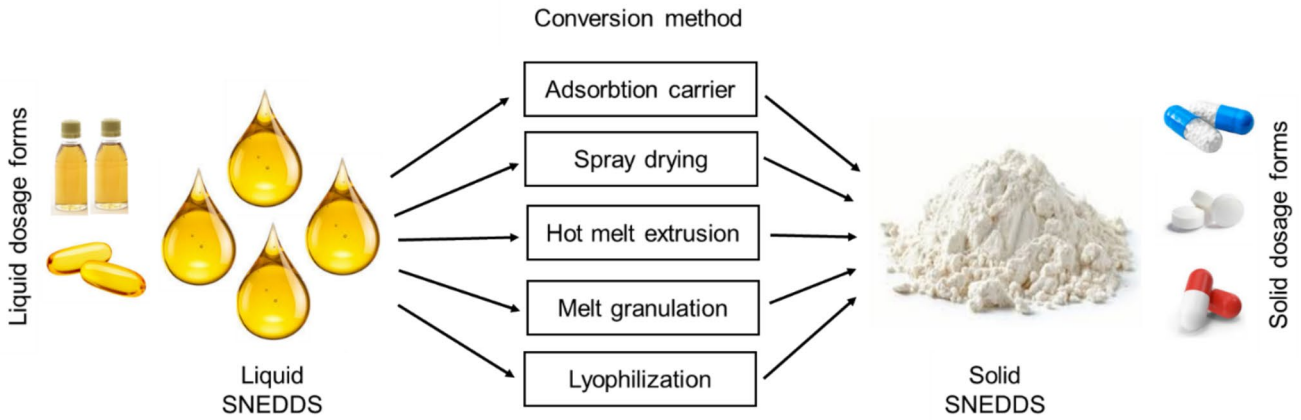

Fig. 3 Liquid to solid conversion of SNEDDS

Table II Examples and Outcomes of Solidification Methods Using Different Carriers for Solid SNEDDS Formulation

Formulation	Solidification method	Advantages	Disadvantages	**References**
Flurbiprofen Labrafil (13 %)/Labrasol (81 %)/Transcutol (7.5 %)	Spray drying with silicon dioxide as carrier	Smaller particle sizes (<100). Amorphous state. Increased dissolution rate and oral bioavailability.	N/A	(83)
	Spray drying with Magnesium stearate as carrier	Eutectic mixture formed. Increased dissolution rate and oral bioavalaibility.	Large particle size	
	Spray drying with polyvinyl alcohol (PVA), sodium carboxymethyl cellulose (Na-CMC) as carrier	Solid dispersion/microcapsule formed. increased plasma concentration.	Solid SNEDDS not formed Dissolution rate not improved	
	Spray drying with hydroxypropyl-β-cyclodextrantrin (HP-β-CD) as carrier	Solid dispersion formed. Improved dissolution rate.	Solid SNEDDS not formed No significant increase in oral bioavailability	
Celecoxib (Miglyol® 812 (27 %)/Tween® 80 (46 %)/elucire® 44/14 (4 %)/d-TPGS (6 %)	Hot melt extrusion with aminomethacrylate-based copolymer as carrier	Amorphous form Excellent saturation solubility. Particle size < 50	Decreased drug solubility. Similar release profile to liquid SNEDD.	(30, 31)
Efavirenz, Tween® 80 (24 %), d-TPGS (3 %), PM-100 (19 %), Transcutol® HP (28 %)	Hot melt extrusion with affinisol® HPMC 100 LV as carrier	Amorphous form High drug loading Particle size < 50	Low screw speed used during extrusion. Decreased initial drug release	
Fenofibrate, Miglyol® 812 (17 %), Brij® 35 (9 %), Tween® 80 (50 %), and d-TPGS (10 %)	Hot melt extrusion with Kollidon 17 PF as carrier	Amorphous form High drug solubility Particle size < 50	Drug release only increased slightly	

tends to be (26). This can also prevent agglomeration when converted to solid SNEDDS as has been reported when exposed to higher temperatures (31). Both liquid and solid SNEDDS can precipitate before absorption by interfering with drug nucleation and crystal growth or by changing the properties of the aqueous medium (37). Increasing the concentration of surfactants can reduce precipitation; however, it can also cause severe stomach irritation and toxicity. Additionally, if the surfactant is used/increased because of its solubilization property, there is often a possibility of precipitation because the dilution of the nano-emulsion in the stomach will decrease the solvation capacity of the formulation (10). Therefore, precipitation inhibitors such as polymers, cyclodextrins, and solid carriers are used in SNEDDS formulations (37, 69, 93). These excipients work by delaying the rate of drug nucleation and crystal growth through stearic hindrance, hydrogen bonding, hydrophobic interactions and reducing the SNEDDS viscosity (94). Another strategy to circumvent drug precipitation and compensate for the poor absorption it causes includes the implementation of supersaturated SNEDDS/super-SNEDDS. In super-SNEDDS (sSNEDDS), a drug concentration above the solubility equilibrium is added to the formulation to achieve better drug solubility, GI stability, and absorption.

pH environment is also a critical concern for liquid and solid SNEDDS stability. Orally administered drugs can have pH-dependent drug solubility, which can lead to drug precipitation in varying GI environments, thus, SNEDDS should be able to self-emulsify and maintain their nano size irrespective of the pH in the GIT (95). A study by Shahba *et al*., revealed that the self-emulsification of fatty acid-based SNEDDS was negatively affected as the pH increased to a more alkaline state with cinnarizine (weak base) as the active drug (96). The researchers concluded that oils with lower acid values or oils that develop surfactant/co-surfactant properties as pH changes (e.g. oleic acid) may withstand drug precipitation at higher pH (96). Other studies have also reported a change in size and zeta potential as the pH changes (95, 97). Additionally, it has been suggested that the presence of bile salts in the GIT can facilitate the decrease in nano-emulsion droplet size (98, 99). Precipitation inhibitors such as hydroxypropyl methylcellulose and polyvinylpyrrolidone can adsorb into the drug crystal surface and reduce the rate of crystallization.

The poor permeation and quick degradation of protein and peptide drugs in the GI makes them a good candidate for SNEDDS formulation. However, the poor solubility of proteins in oils makes this approach challenging; moreover, the temperature-reliant conversion methods of

SNEDDS also make it difficult for protein-based SNEDDS solidification. Unlike small hydrophobic drugs, proteins/peptides don't naturally partition into the oil phase. To overcome this, strategies such as ion pairing, amphiphilic carriers, and selection of co-solvents that solubilize the drug, have been employed to adapt SNEDDS for protein/peptide delivery (100–102). Studies such as that of Bahiraei *et al*. and Soltani *et al*., have successfully used cationic derivatives of cyclodextrins to develop ion-paired hydrophobic complexes with negatively charged heparin molecules (100, 102). Another study reported the design of protein-based liquid SNEDDS by preparing a solid dispersion of β-lactamase protein with soy phosphatidyl choline (an amphiphilic carrier) and then dissolving this solid dispersion into the oil phase of the SNEDDS (98). The authors reasoned that the amphiphile would surround the protein to form a micelle structure in the oil, so that the protein could be dissolved in the oil (98). Some studies have also increased insulin solubility in SNEDDS by employing complexation with phospholipids. However, absorption still remained suboptimal (103, 104). Moreover, maintaining the activity of protein/peptide drugs within SNEDDS systems is paramount. A study by Friedl *et al*. demonstrated that papain – a model protein drug- showed no activity after 48 hours of storage in liquid SNEDDS, but showed activity in solid SNEDDS after the addition of adsorbents and solidification in solid SNEDDS (75). The results emphasized the need to develop solid SNEDDS that stabilize protein drugs (105).

Beyond the tests applied to liquid SNEDDS, such as droplet size, PDI, and emulsification time, solid SNEDDS require additional evaluation to confirm their structural integrity and functionality. Solid-state techniques such as powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Raman, and infrared spectroscopy are used to examine crystallinity, polymorphic transitions, and drug-excipient interactions, while scanning electron microscopy (SEM) and transmission electron microscopy (TEM) provide insights into morphology. These analyses are critical for ensuring stability and optimizing formulation performance. Moreover, for successful processing into capsules or tablets, solid SNEDDS powders must demonstrate adequate flow and compressibility. This is typically assessed using parameters like angle of repose, Carr's index, and Hausner's ratio, which help predict uniformity and suitability for large-scale manufacturing (26, 106, 107).

In Vivo and *In Vitro* Behaviour

Some studies have reported that there is no significant difference between the dissolution profiles of liquid SNEDDS and solid SNEDDS powder (70, 82, 108–111). Ultimately, dissolution results for liquid and solid SNEDDS can vary based on composition, drug properties, and solidification method (80, 112). The difference only becomes more significant when comparing liquid SNEDDS to solid final dosage forms such as tablets and pellets. The disintegration and deaggregation process encountered during the dissolution process of the solid SNEDDS can slow the rate of drug dissolution (113). Furthermore, the adhesion interaction between lipid components and the adsorbent particles of the solid SNEDDS can reduce the rate of dissolution (114). For such reasons, drug release of liquid SNEDDS is faster than that of solid SNEDDS (115, 116). Notably, the release rate is still higher for solid SNEDDS compared to conventional solid counterparts because the inclusion of an adsorbent increases the surface area and porosity for the quick disintegration of the solid particles (112). Because liquid SNEDDS are already in a dispersed state and readily form nano-emulsions upon exposure to GI fluids, they have a quicker initial rate of absorption and, therefore, quicker onset of action than solid SNEDDS (112). Essentially, solid SNEDDS may be more beneficial in diseases where controlled or sustained drug release is needed and where drug stability within the SNEDDS formulation is pivotal.

The droplet size and PDI are greatly dependent on the solidification technique used as well as the type of solid carriers. Liquid SNEDDS are absorbed in the pores of the solid carrier by attaching to the surface of the adsorbent (117). This process can increase the droplet size, further decreasing the SNEDD's absorption. Therefore, liquid SNEDDS tend to have smaller droplet sizes, or a negligible difference compared to solid SNEDDS, though this varies in the literature. Water-based and non-ionic carriers are preferable in maintaining solid SNEDDS droplet size. High pressure homogenization has been used to decrease the droplet size of solid SNEDDS prepared by porous carriers (118, 119). Spray dried solid SNEDDS powder show more rapid dispersion during dilution in water than the adsorbent counterpart (111). Hydrophobic carriers also show better results of particle size and zeta potential compared to that of hydrophilic carriers (111, 120). Thus, the selection of carrier is an important factor in the development of solid SNEDDS, since the carriers exhibited significant effects on the crystalline properties, dissolution and oral bioavailability of flurbiprofen and on the formation of solid SNEDDS.

The absorption/cytotoxicity of solid and liquid SNEDDS compared to their conventional counterpart is unclear. Some studies have reported improved cell toxicity, and others report improved absorption but maintained cytotoxicity (47, 120–122). Despite some results on poor correlation between *in vitro* models and *in vivo* studies of liquid and solid SNEDDS (4, 123), several studies have reported good correlation when relevant models are used. For example, the *in vitro-in vivo* correlation module of GastroPlus™ simulation showed a good correlation between *in vitro* release and

in vivo absorption, with a predicted systemic absorption of ~96.5% model in rats (56, 124).

Using Artificial Intelligence (AI) to Optimize Liquid and Solid SNEDDS Formulations

Formulating SNEDDS encompasses several considerations and bottlenecks as discussed in this review. Conventional Design of Experiments (DoE) such as ternary phase diagrams and Box-Behnken designs used to obtain SNEDDS, possess several challenges in terms of data handling, adaptability and efficiency. DoE only works best with pre-defined experimental factors and ranges with decreasing accuracy as formulation parameters are moved beyond the original design space, and the tool requires multiple iterations to fine-tune results. With challenges such as these, researchers are seeking better alternative tools to optimize liquid and solid SNEDDS. As AI has shown rapid advancement recently, various *in silico* tools have been adopted and optimized to streamline pharmaceutical formulations and their processing. Currently, AI tools such as machine learning (ML) and deep learning (DL), can analyze large databases of oils, surfactants, and co-solvents to predict the solubility of poorly soluble drugs, recommend compatible excipient combinations and optimise component ratios to enhance stability and drug loading. Moreover, DL tools can combine qualitative and quantitative data sets using multiple neural network layers to extract increasingly complex features from data (e.g., molecular descriptors, excipient fingerprints). A recent study explored the use of AI in the formulation of SNEDDS for the delivery of anacardic acid (125). The researchers successfully used a predictive ML model to identify an improved SNEDDS system with olive oil, Tween 80, Tween 20, glycerol, and soy lecithin as SNEDDS components. Relevant characterisation methods were employed, which confirmed the development and feasibility of the formulation.

Ternary phase diagrams and Box Behnken designs can also be modelled to automatically identify nano-emulsion regions, which replaces labour-intensive automatic mapping. For example, one study described the integration of conventional Computer-Assisted Logic for Phase Diagrams as training data to generate ML algorithms (126). Although their study was not focused on SNEDDS, the authors reported success in predicting the phase diagram of a material with similar multicomponent systems. This same approach could be applied to predict the characteristics of SNEDDS, such as droplet size, self-emulsification time, zeta potential, stability and *in vitro* performance. This reduces the number of experimental trials needed.

Bayesian Optimization is an optimization algorithm that typically uses a Gaussian Process (GP) or similar surrogate model to approximate the unknown relationship between inputs and outputs (127–129). Using excipient descriptors (HLB, log P, chain length, polarity index), Bayesian Optimization may predict which excipient combinations are worth testing in SNEDDS formulations. Unlike DoE, Bayesian Optimization does not assume a polynomial relationship—it updates its predictions based on observed data (130). This can save lab resources and accelerate formulation development in SNEDDS formulations. Deep learning tools such as Artificial Neural Networks (ANNs) can predict formulation performance even with multiple interacting excipient properties (HLB, polarity, solubility parameters) that would overwhelm a traditional DoE model (131, 132). A study was conducted to compare the model-dependent DoE I-optimal design approach to ANN technique with respect to the minimum globule size of SNEDDS with selected excipients (132). The study revealed that ANN provided better predictability for the selected output parameter, where the final globule size of the SNEDDS formulation was closer to that obtained using ANN optimization than conventional DoE (132).

Support Vector Machines (SVMs) are another machine learning algorithm that can separate and classify data points or predict continuous outcomes using optimal hyperplanes. In the case of SNEDDS, SVM may be used to classify excipient combinations into "likely to self-emulsify/solubilise drug/produce small droplets" *vs*. "unlikely" groups before physical testing (133). However, a drawback in the adaptation of SVM in SNEDDS formulation is that it can only handle small-to-moderate datasets. This can be a significant limitation when dealing with the vast datasets often used in SNEDDS development and optimization.

Genetic Algorithms (GAs) explore the parameter space iteratively, "breeding" better solutions, and unlike conventional ternary phase diagrams or Box-Behnken designs commonly used in SNEDDS formulations, GA is not limited to a fixed design space with defined factor ranges set before experimentation. The tool can be used to optimize multiple, competing targets in SNEDDS (e.g., smallest droplet size + highest drug loading + fastest emulsification) simultaneously (134, 135). For example, Daware *et al*. was successful in using GA screening to illustrate the correlation between droplet size and various molecular descriptors of a drug in a SNEDDS system (134).

An AI tool that does not rely on numerical factor levels is Random Forests (RFs). RFs use an ensemble of decision trees to vote on the best prediction, useful for ranking variable importance (136). RF naturally handles categorical and continuous variables without the need for transformation (133). This is important in SNEDDS optimization where excipient characteristics influence factors such as droplet size and stability. Conventional DoE usually requires numerical factor levels and may not easily handle qualitative factors like excipient type.

Table III Application/potential Applications of AI at Various Stages of SNEDDS Formulation

Formulation stage	AI application	AI tools/techniques	Potential outcome	Examples	References
Excipient selection	Predict optimal oils, surfactants, co-solvents and drug candidate.	QSAR models, Random Forest, SVM, Deep Learning, Genetic algorithm	Enhanced solubility, drug loading, and stability	Study investigated the significance of > 700 physiochemical properties/molecular descriptors of 40 drug molecules on droplet size.	(133, 134)
Component compatibility	Forecast excipient-drug and excipient-excipient interactions	ANN, Support Vector Regression	Reduced formulation failures and accelerates screening	Study compared ANN to DoE and proved that ANN had superior predictability of output for given input of SNEDDS variables.	(125, 132)
Ternary diagram prediction	Automate nano-emulsion region mapping	Bayesian Optimization	Minimize experimental workload in SNEDDS region identification	Study used Bagging-based regression techniques to predict the solubility of raloxifene and the density of carbon dioxide (CO_2).	(127–129).
Droplet size & stability prediction	Predict droplet size, PDI, zeta potential and drug solubility.	Artificial Neural Networks (ANN), Decision Trees	Enable rapid optimization of nano-emulsion properties	Study used ANNs to predict the apparent degree of supersaturation from two supersaturated lipid-based formulations.	(131, 137, 138)
Emulsification time optimization	Model self-emulsification behavior	Regression models, ML ensembles	Improve robustness and efficiency of liquid SNEDDS	A quadratic model was identified as the preferred model to illustrate various physicochemical parameters of SNEDDS systems with different surfactant types.	(6, 139)
Solid carrier selection	Select optimal solid carriers	ML on physicochemical data (surface area, porosity, etc.)	Ensure stable, flowable, high-loading solid SNEDDS	N/A	N/A
Solidification method selection	Choose best solidification method	Supervised Learning Models	Enhance scalability and product quality	N/A	N/A
Drug-carrier compatibility	Predict interaction and physical stability of drug with solid carrier	Data mining from DSC, FTIR, Raman spectra	Maintain amorphous form and prevent recrystallization	N/A	N/A
Dissolution & bioavailability prediction	Forecast release profile and GI behavior	PBPK modeling, Monte Carlo Simulations	Predict *in vivo* performance without extensive animal testing	Study used PBPK to predict the optimal place in the GI tract for the delivery of a self-emulsifying based system loaded with simvastatin.	(140)
Performance optimization	Iterative model-based refinement of formulation	Reinforcement Learning, DoE-enhanced ML	Accelerate QbD-compliant development	Study proposed a phase diagram prediction method which integrates machine learning algorithms with CALPHAD descriptors.	(126)

Table IV List of SNEDDS Formulations Currently Available on the Market

Drug name	Excipients	Dosage form	Reference
Restasis® (Cyclosporine)	Castor oil, glycerin, polysorbate 80	Liquid eye drops	(156)
Sandimmune® (Cyclosporine)	Corn oil, ethanol, propylene glycol	Liquid sealed in soft gelatin capsules.	(157)
Neoral® (Cyclosporine)	Polyoxyl 40 hydrogenated castor oil, ethanol, propylene glycol	Oral solution	(158)
Norvir® (Rotanivir)	Oleic acid, Cremophor®-EL, ethanol	Liquid sealed in soft gelatin capsules.	(3)
Accutane® (Isotretinoin)	Hydrogenated soybean oil flakes, hydrogenated vegetable oil, soybean oil Olive, polyoxyethylated oleic glycerides, ethanol	Liquid sealed in soft gelatin capsules.	(159)
Rapamune® (Sirolymus)	Soy fatty acids, Tween® 80, ethanol, propylene glycol	Oral solution	(160)
Aptivus® (Tipranavir)	Mono/di-glycerides of caprylic acids, Cremophor® EL ethanol, propylene glycol	Liquid sealed in soft gelatin capsules	(161)

In solid SNEDDS, AI-driven simulations have the potential to optimize solidification methods such as spray drying, freeze drying, or hot melt extrusion by predicting how process variables (e.g., inlet temperature and feed rate) affect yield, particle size, and dispersibility. AI may predict the most suitable solid carriers based on properties like surface area, porosity, and compatibility. Once solidified, AI models can assess the expected dissolution profile and drug release kinetics of the solid SNEDDS using *in silico* tools like physiologically based pharmacokinetic (PBPK) modelling. This predictive power facilitates the development of robust, scalable solid SNEDDS formulations with consistent performance, paving the way for more efficient commercialization of poorly water-soluble drugs. Table III shows a summary of how AI can be used in various stages during the formulation of SNEDDS. The application of AI in this context has been focused on the design of liquid SNEDDS, however studies have not yet explored how these *in silico* approaches can also optimize solidification technique and carrier selection in the design of solid SNEDDS.

SNEDDS Applications

Soft gelatines are at the forefront of liquid SNEDD encapsulation, however, these capsules are prone to several drawbacks such as high production cost, poor stability, and low drug loading. Some researchers have explored liquid SNEDDS as suspensions (141, 142), inhaled aerosols (143), and eye drops (144). Additionally, there has been a new focus on converting commercial intramuscular formulations to oral SNEDDS, in attempt to improve patient compliance (145, 146). Solid formulations also form a substantial portion of SNEDDS delivery. They can be designed as free-flowing powders, tablets, granules, pellets, solid dispersions, microspheres and nanoparticles (26, 147).

Because of the high solubility and dissolution capacity of liquid and solid SNEDDs, they have recently been explored as fixed-dose combinations for multiple drugs. Candesartan cilexetil and hydrochlorothiazide have been formulated as SNEDDS in the liquid form, while another study explored candesartan, glibenclamide, and rosuvastatin in SNEDDS and supersaturated SNEDDS in the solid form using a syloid adsorbent (109, 148). Both outcomes yielded improved solubility and dissolution rates, however, researchers who investigated the solid SNEDDS acknowledged a need for further *in vivo* studies to confirm the oral bioavailability and therapeutic efficacy of the SNEDDS.

Developing mucoadhesive SNEDDS has also gained attention recently. The method involves the thiolation of SNEDDS with polymers such as Pluronic®, and chitosan and/or coating the formulation with stronger muco-adhesives like alginate and Carbopol® to enhance muco-adhesion, muco-penetration and site-specific delivery (149). This kind of formulation offers an alternative to solid SNEDDS where researchers can escape complex SNEDDS solidification processes and prolong the drug's gastric exposure. Stimuli-responsive SNEDDS may also garner interest in the future. So far, one study has formulated pH-sensitive SNEDDS containing acid-labile silibinin as a model drug. The aim was to protect the drug from acidic degradation in the stomach while enhancing drug release in the small intestines through emulsification of the liquid SNEDDS at a pH of 7–9 (150). The authors also reported an increased *in vitro* release profile compared to that of conventional powder and tablet dosage SNEDDS. However, pH-sensitive SNEDDS in the liquid form have not been thoroughly investigated, possibly because they beg the concern of poor targeting since their self-emulsification is a gradual pH-dependent process which begins from the GIT, meaning drug release is minimal, not absent at gastric areas with lower pH values, and it will gradually increase until it reaches the targeted site.

Poorly soluble anticancer agents commonly used intravenously have also been explored in an attempt to formulate SNEDDS-based oral dosage forms (151, 152). Because existing chemotherapeutic agents such as paclitaxel, contain

Table V SNEDDS Patents From 2020-2025

Patent (year)	Company	Composition	SNEDDS state & dosage type	Reference
WO2021239798 (2021)	Evonik Operations GmbH	The patent focuses on methacrylic copolymer matrices to form solid SNEDDS with good reconstitution	Solid SNEDDS — powder/extrudate/tablet embodiments described.	(162)
WO2022108572A1/ WO2021076081 family (2021–2022	Evonik Operations Gmbh	SNEDDS containing bosentan monohydrate using long-chain mono and diglyceride mixtures.	Liquid SNEDDS (nanoemulsion; droplet size <50 nm, PDI <0.2) with demonstrated conversion into solid/powder & tablet forms in examples.	(163, 164)
WO2022184549A1 (2022)	Evonik Operations Gmbh	**Dimethylaminoethyl methacrylate–butyl methacrylate–methyl methacrylate copolymer-based matrix as an adsorbent for solid SNEDDS.**	Solid – powder/extrudate/tablet embodiments described.	(165)
WO2023240348A1 (2023)	Empowerpharm Inc.	Intragranular SNEDDS includes cannabinoid + solubilizing agents (e.g., alcohols C8–C18, glycerides, polyoxylglycerides) + nonionic surfactants + oil.	Solid – tablets (intragranular SNEDDS adsorbed on porous salt)	(166)
US11547690B1 (2023)	King Abdulaziz University	Chemotherapeutic drug-loaded SNEDDS systems	Liquid SNEDDS and formulations converted to solid forms described	(167)
US11253481B1 (2022)	King Abdulaziz University	Glimepiride and/or Rosuvastatin in a curcuma-oil-based SNEDDS.	Semisolid/semisolid-ink SNEDDS for 3D-printing → final dosage = 3D-printed tablets. (Viscous semisolid ink that self-nano-emulsifies on contact with aqueous media once printed and dried)	(168)
BR102024000877A2 (2024)	Aparecida Medeiros Maciel Maria	Anacardium occidentale L. tannins (natural extract for COVID-19)	Liquid SNEDDS	(169)
EP4529919A1 (2023)	Evonik Operations GmbH	Solid SNEDDS using biosynthetic cellulose as adsorbent	Solid SNEDDS— powder form	(170)

high concentrations of surfactants which can be toxic, SNEDDS are useful in efficiently decreasing the surfactant concentration to obtain high drug solubility. As technology advances and the need for customized drug release profiles increases, SNEDDS are being integrated into 3D-printed pharmaceuticals. PAM-based printing has been used to design tablet dosage forms of SNEDDS containing dapagliflozin which enhanced drug solubility and enabled tablet-size-altering by simply modifying printing dimensions (153). The same researchers further explored 3D printing using FDM-printed shell design for individualized doses that healthcare practitioners can prepare themselves. They proposed that the molten SNEDDS formulation could be filled into their novel FDM-printed shell design, which subsequently surrounds the solidified content for enhanced formulation protection (154).

Despite the advancement of SNEDDS formulations in the literature, only a few formulations have been commercialized. Furthermore, several reports have demonstrated some hypersensitivity reactions as side effects, presumably related to types of surfactants and oils. Cremophor EL has been known to cause GI toxicity and ocular discomfort has been reported in Restasis® (155). A list of the SNEDDS formulations currently available on the market is provided in Table IV. As seen in the Table, all available formulations are in liquid form, highlighting a market gap in the exploration of solid SNEDDS. Furthermore, we summarise notable liquid and solid SNEDDS patents obtained within the past 5 years with their unique constituents in Table V.

Conclusion and Future Perspectives

The design of liquid and solid SNEDDS has seen increasing exploration over the years. However, the primary last-stop dosage form for SNEDDS remains liquid in gelatin capsules or oral solutions. As researchers have observed the difficulty in maintaining the stability of liquid SNEDDS, its conversion to a solid state is gaining more interest. Nonetheless, the preparation complexities and increasing dosage volume involved in converting liquid SNEDDS to solid SNEDDS are disadvantages of its exploration and a hindrance to its commercialization. Researchers must weigh the advantages of the stability of solid SNEDDS against the better absorption of liquid SNEDDS before making verdicts on their final dosage form. For both liquid and solid SNEDDS, precipitation inhibitors or the use of super-SNEDDS should be considered to enhance drug stability in the GI.

Looking ahead, the integration of artificial intelligence and machine learning with experimental formulation design is poised to accelerate the identification of optimal excipient combinations and predict long-term stability outcomes. Moreover, there is increasing interest in extending SNEDDS beyond small hydrophobic molecules to more complex therapeutic classes, including peptides, proteins, and nucleic acids, using strategies such as ion pairing and amphiphilic carriers. The integration of innovative solidification techniques or exploration of solidification parameters that support such fragile molecules is also essential in the advancement of solid SNEDDS. Overall, the future of both liquid and solid SNEDDS lies in their continued evolution into smarter, more stable, and patient-friendly platforms that are adaptable across drug classes, manufacturing scales, and clinical needs.

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