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**Review Article**

## Self-Nanoemulsifying Drug Delivery System: Liquid, Supersaturable, and Solid Dosage Forms

Ishraq Kadhim Abbas* (ID)

*Department of Pharmaceutics, Faculty of Pharmacy, Al-Rafidain University College, Baghdad, Iraq*

**Abstract**

A third of recently created drugs have poor water solubility and absorption. Innovative methods, such as self-nanoemulsifying drug delivery systems (SNEDDS), are being developed to address issues with pharmaceutical delivery and bioavailability. These systems, which are referred to as isotropic mixtures, are made up of the drug, a suitable oil, a surfactant, and either a co-surfactant or co-solvent. These elements combine to create a "oil in water (O/W)" nanoemulsion after being lightly stirred. Colloidal systems, including microemulsions and nanoemulsions, are being used more commonly in food, cosmetics, and pharmaceutical preparations to encapsulate, protect, and transport lipophilic components. The nanoscale particles used in these kinds of delivery systems have a number of potential benefits, including enhanced long-term stability, enhanced solubility, enhanced optical transparency, and enhanced bioavailability. To create SNEDDS, one can utilize a phase diagram technique or statistical design of trials. For SNEDDS, switching from a liquid to a solid dose form may have improved stability as well as increased patient compliance. The design and production of SNEDDS and their effects on the bioavailability of several medications are the subject of numerous studies that are included in this review.

*Keywords*: Bioavailability, Solubility, Self-nanoemulsifying drug delivery system, Oral bioavailability.

**نظام توصيل الأدوية ذاتي الاستحلاب: أشكال جرعات سائلة وفائقة التشبع وصلبة**

**الخلاصة**

ثلث الأدوية التي تم إنشاؤها حديثا لديها قابلية ضعيفة للذوبان في الماء والامتصاص. ويجري تطوير أساليب مبتكرة مثل نظم توصيل الأدوية ذاتية الاستحلاب النانوي SNEDDS لمعالجة المسائل المتعلقة بإيصال المستحضرات الصيدلانية والتوافر البيولوجي. تتكون هذه الأنظمة، التي يشار إليها باسم مخاليط الخواص، من الدواء، وزيت مناسب، وخافض للتوتر السطحي، وإما خافض للتوتر السطحي أو مذيب مشترك. تتحد هذه العناصر لتكوين مستحلب نانوي "زيت في الماء" بعد تحريكه برفق. تستخدم الأنظمة الغروية، بما في ذلك المستحلبات الدقيقة والمستحلبات النانوية، بشكل أكثر شيوعا في الأغذية ومستحضرات التجميل والمستحضرات الصيدلانية لتغليف المكونات المحبة للدهون وحمايتها ونقلها. تتمتع الجسيمات النانوية المستخدمة في هذه الأنواع من أنظمة التوصيل بعدد من الفوائد المحتملة، بما في ذلك الاستقرار المعزز على المدى الطويل، والذوبان المعزز، والشفافية البصرية المحسنة، والتوافر البيولوجي المحسن. لإنشاء SNEDDS، يمكن للمرء استخدام تقنية مخطط الطور أو التصميم الإحصائي للتجارب. بالنسبة إلى SNEDDS، قد يؤدي التحول من شكل جرعة سائلة إلى شكل جرعة صلبة إلى تحسين الاستقرار بالإضافة إلى زيادة امتثال المريض. تصميم وإنتاج SNEDDS وتأثيراتها على التوافر البيولوجي للعديد من الأدوية هو موضوع العديد من الدراسات التي تم تضمينها في هذه المراجعة.

* *Corresponding author*: Ishraq K. Abbas, Department of Pharmaceutics, Faculty of Pharmacy, Al-Rafidain University College, Baghdad, Iraq; Email: ishraqalmualla@yahoo.com

## INTRODUCTION

Oral drug delivery is the favored method for both patients and manufacturers due to its safety, patient compliance because it is self-administered, and greater flexibility in terms of developmental requirements [1]. About 70% of all recently discovered drug candidates have poor water solubility and are lipophilic. Drugs having low oral bioavailability—which can result in poor and inconsistent therapeutic outcomes—are more likely to have low water solubility. By employing the proper medicine formulation, this can be avoided [2]. Medication classification is divided into four classes by the biopharmaceutical classification system (BCS) (I, II, III, and IV). Classes II and IV among these groupings are characterized by low hydrophilicity and hence low water solubility. As a result, oral administration of pharmacological drugs is affected by factors such as low solubility, variable absorption, and limited bioavailability in addition to inter- and intra-subject variability. Additional factors affecting oral bioavailability include poor drug permeability through gastrointestinal tract (GIT) membranes, susceptibility to interactions with food and/or medications, the potential for GIT acid or enzyme degradation, and, in rare circumstances, the effects of first-pass metabolism [3-5]. Solubilization of the medicine is crucial for drug absorption from the GIT since partial solubility of the active component may cause low permeability and insufficient drug bioavailability, which produce considerable discrepancies after administration of the product orally [6]. To enhance drug dissolution and solubility of poorly soluble drugs and thereby increase bioavailability, a variety of techniques have been used, including the use of surfactants, solubilizers, cosolvency, hydrotrophy, and novel excipients. These techniques include the use of liposomes, micelles, nanoemulsions, microspheres, polymer nanoparticles, inorganic nanoparticles, salt formation, solid dispersions, and others. Among them, lipid-based formulations have shown to be advantageous, with notable gains in the solubility and bioavailability of numerous active components, including proteins, nutritional supplements, and lipophilic medicines [6–12]. Liposomes, solid-lipid nanoparticles, drug-lipid conjugates, micelles, nanoemulsions, and self-nanoemulsifying drug delivery systems (SNEDDSs) are a few examples of lipid-rich formulations [13]. With an emphasis on the potential effects of the excipients used in SNEDDS formulation, which may increase the solubility and bioavailability of pharmaceuticals intended for oral administration, this review article gives an outline of the development of SNEDDS. This research examines numerous challenges related to the production of liquid SNEDDS, in addition to supersaturated formulations and conventional solidification techniques for SNEDDS, to boost the capacity of drug-loading.

## Overview of Self-Nanoemulsifying Drug-Delivery Systems

Similar to lipid formulations, isotropic self-emulsifying drug delivery systems consist of the right oils, surfactants, and occasionally co-solvents that, when in contact with water and gently swirled, spontaneously emulsify into an O/W emulsion. Self-emulsification occurs when the energy required to increase the dispersion surface area is greater than the favorable circumstances for an entropy-altered dispersion. Later on, such a system was given the names self-microemulsifying (SMEDDS) and self-nanoemulsifying (SNEDDS) systems [14,15]. Self-emulsifying systems can be modified empirically by experimenting with various component types and modifying their ratios, or by utilizing a ternary phase diagram [14,15]. Bahloul *et al*. (2014) created a contemporary approach utilizing coupled hydrophilic lipophilic balancing to apply a response surface methodology (RSM) (HLB). By lowering the number of trials necessary to design a self-emulsifying delivery system with adequate drug release of active pharmaceutical components and enhanced pharmacokinetic indices, this strategy may save time and money [16,17]. The bioavailability, solubility, and dissolution of lipophilic active components, particularly those falling within classes II and IV of the biopharmaceutical classification system, have shown considerable improvements with self-emulsifying systems [18]. This is as a result of these systems' higher isotropic characteristics and lower surface-area free energy. Self-emulsifying systems are effective peptide and protein transporters because they delay digestion and increase permeability through GIT membranes, according to recent studies [19–21]. A number of methods, including adsorption, spray drying, spheronization, eutectic mixing, capsule filling, extrusion, and melt granulation, have been developed in recent years to transform liquid or semisolid components into dried form (powder) [22,23]. Solidified self-nanoemulsifying systems (S-SNEDDSs) provide several advantages over SNEDDS, including increased patient compliance and improved product stability for manufacturers. Both systems (SNEDDSs and S-SNEDDSs) can significantly alter the drug permeability of drugs across GIT membranes by reducing efflux transporter activity across intestinal cell membranes, preventing chemical and enzymatic degradation of the drug in the GIT medium, and improving drug absorption through direct uptake of the substance through the intestinal lymphatic pathway. It has also been shown that during storage, there is little medicine leakage between the O/W nanosized oily droplets [24]. Unlike other lipid nanocarriers, SNEDDSs are easily scaled up by combining the component parts with affordable machinery, allowing the solution to solidify, and producing a solid dosage form. Additionally, SNEDDSs in GIT medium experience spontaneous fine dispersion. The possibility of product aggregation during storage and abrupt medication release have no impact on this type of delivery method

[25]. The majority of research on self-nanoemulsification to date has focused on the value of SNEDDSs in improving the oral administration of lipophilic active substances. However, only a few studies have shown how important SNEDDSs are for enhancing the oral transport of hydrophilic macromolecules [25].

## General Components of SNEDDSs

Using the Lipid Formulation Classification System, Pouton categorized and identified several lipid-based carriers (LFCS). SNEDDSs are categorized as class III and are made up of a combination of hydrophilic surface-active substances (surfactants and cosurfactants), oils, and, in some cases, cosolvents. The selection of appropriate ingredients determines the best formulation for a SNEDDS. The optimal excipient for the SNEDDS formulation should be chosen with the aid of preformulation experiments for solubility and emulsfication effectiveness [26].

### Active pharmaceutical ingredient

The active pharmaceutical ingredient (API) must be of low dosage and have an acceptable level of lipophilicity. It must consequently be adequately soluble in oils, surfactants, and co-surfactants (co-solvents) approved for use in pharmaceuticals [27]. Surfactants, co-solvents, and oils or lipids are the other two main components of SNEDDS besides API.

### *Oils*

The main raw materials used to make SNEDDSs are oils with medium- and long-chain triglycerides (TG) of various saturation levels. Due to its considerable influence on both drug loading and absorption capacity, the maximal solubility of the medicine in the oil is taken into account when choosing an oil, or if necessary, a combination of oils [28]. As Larsen *et al*. demonstrated by showing that SNEDDS, which comprises oil with the lowest drug solubilization capacity, showed the maximum drug absorption, higher drug solubility in oil is not necessarily the best measure for maximizing optimal in vivo performance and should not be used alone [29]. Direct lymphatic transport absorption and increased drug bioavailability due to improved drug solubility are often the two main advantages of oils. On the other hand, the improved in vivo solubility of a hydrophobic medication in the intestine may be tied to the duodenum's production of cholesterol and bile salts, which once again form micelles, and may explain the improvement in the bioavailability of SNEDDS [30]. The polar groups continue to be on the micelle's aqueous side, while the lipophilic groups remain in the micelle's center. Micelles dissolve when a medication with limited solubility and a lipid component enter the duodenum. Because the formation of lipoprotein enhances the transport of the lipophilic drug by the lymph, it is well known that the lymphatic system may be able to assist SEDDS absorption, avoiding the liver's first-pass metabolism. Both the substances delivered by the lymphatic system and the drug-carrying lipoprotein lipid core reach the systemic circulation [31]. As lipid components in formulations, castor oil, sesame oil, soybean oil, and other natural oils are still acknowledged. However, it's possible that these oils aren't particularly good for emulsifying or loading medications [32]. To improve drug solubility, modified, medium-chain, and long-chain triglycerides are typically employed in SNEDDSs. While medium-chain triglycerides (such Capryol® 90, Captex® 300, and Labrafac® CC) have lipid chains between C8 and C10, long-chain triglycerides (including Maisine®-35, Lauroglycol® 90, Peceol®, and others) include lipid chains longer than C10 [27]. After being consumed orally, triglycerides are changed into monoglycerides, diglycerides, and fatty acids by pancreatic and stomach lipases. Endogenous lipids from the gall bladder, including bile salt, lipoprotein, phospholipid, and cholesterol, are produced as a result of the latter breakdown products. The solubility and absorption of the medicine are improved across the GIT by producing micelles once those products reach the small intestine [31,33,28]. Because of their enhanced capacity for self-emulsification and solubilization, medium-chain triglycerides are favored [34]. They can improve drug transport via the portal vein but have little potential to stimulate drug transport via the lymphatic system [35,36]. On the other hand, long-chain triglycerides accelerate drug transport through lymph arteries because they bypass first-pass metabolism in the liver and are directly encapsulated into chylomicrons before being delivered into the lymphatic system [36,37]. Long-chain triglycerides might be challenging to emulsify at times [38]. As a result, it is possible to create desirable characteristics and improve pharmacokinetics by combining medium- and long-chain triglycerides.

### *Surfactants*

Amphiphilic surfactants are found at the O/W interface and aid in increasing the stability of nanoemulsions by lowering surface tension. They are divided into ionic (anionic, cationic, and zwitterionic) and non-ionic surfactants based on the charge they carry. Non-ionic surfactants are employed more commonly because of their lower toxicity and improved nano-emulsion stability over a larger pH and ionic strength range [24]. Based on their lipophilicity, surfactants are further categorized into lipophilic (HLB 3-6), which creates water/oil emulsion, and hydrophilic (HLB 8–16), which creates oil/water emulsion. Since they have been proven to be safer, non-ionic surfactants are frequently preferred over ionic surfactants. The most popular non-ionic surfactants with HLB > 12 allow spontaneous nano-emulsification with particle sizes of less than 200 nm after being diluted in an aqueous solution [39]. It's important to consider a surfactant's ability to emulsify, the hydrophilic-lipophilic balancing value, and its maximum drug solubilization while selecting one for SNEDDSs. The effect of surfactant

concentration on emulsion particle size has previously been demonstrated [40]. Raising the surfactant concentration may produce smaller emulsion droplet particles by reducing interfacial surface tension and the free energy for emulsification [40]. The O/W interface may now be disrupted and larger emulsion droplets could occasionally arise from adding more surfactant [41,42]. This is because water could now enter lipids more easily. Another important characteristic of nonionic surfactants like Tween® 80 and Cremophor® EL is their capacity to promote membrane fluidity and block efflux transporters, both of which are essential elements in increasing drug bioavailability [42,43]. These surfactants must exhibit acceptable safety profiles due to the potential irritation they may cause to the GIT epithelium [44]. It is advised to keep the surfactant concentration as low as possible. In the creation of SENDDSs, either a single surfactant or a combination of surfactants can be used to obtain the desired properties. A few examples of frequently used nonionic surfactants for SENDDS preparation include a variety of solid or liquid ethoxylated polyglycolyzed glycerides (like cremophor EL), polyoxyethylene sorbitan fatty ester (tween family), polyethylene oxide-polypropylene oxide block copolymers (pluronic family), and polyalcohol esters of fatty acids like solutol HS15 and labrasol. Oil and surfactants are heatedly mixed together, and then deionized water is added to generate isotropic mixtures. Once the system has reached equilibrium, transmittance may be determined using a spectrophotometer, and sizer zeta can be used to determine the droplet size and polydispersity index [47].

### *Cosurfactants/Cosolvents*

A cosurfactant, additional surfactants, or occasionally a cosolvent is required because it is uncommon for one surfactant to be able to provide low interfacial tension. The stability and homogeneity of the nanoemulsion will be improved by co-surfactants' ability to cooperate with surfactants to enhance surfactant dispersibility in the oil and eventually the solubility of drugs. Co-surfactants also contribute to a greater capacity for drug loading [48]. A second surfactant would also normally result in a very slight reduction in interfacial tension and may possibly momentarily dip to a negative value, at which time the interface would open up to produce finely dispersed droplets [49]. Cosurfactants, on the other hand, can get beyond the surfactant coating and increase fluidity at the oil-water interface. Vacuum spaces between the surfactant molecules could emerge from this. Surfactants and cosurfactants are preferentially adsorbed at interfaces to minimize interface energy, provide mechanical barriers to coalescence, and promote the thermodynamic stability of nanoemulsion formulations [50]. To create a stable self-nano emulsion, the required free energy must be extremely negative [51]. Surfactant type and concentration are essential for reducing the free energy of formulation, raising the entropy of the dispersion system, and reducing interfacial tension, which leads to the rapid formation of

nanoemulsions. By increasing interfacial fluidity, the use of cosurfactants or cosolvents lowers the concentration of surfactant required, minimizes the possibility of local surfactant irritation, and reduces dosage variation [52]. The weight ratio of the surfactant to the cosurfactant or cosolvent has no discernible impact on the amplitude of the nano-emulsion, area, or size distribution [53,54]. Cosolvents that are frequently used are Transcutol®, HP, glycofurol, and others. A lot of PEG, glycol, ethanol, and other substances are employed [55,56]. Due to the ease with which cosolvents could transfer into the water phase after the aqueous dispersion, their amount should be kept to a minimum to prevent the medication from precipitating [57]. Additionally, the volatile cosolvents or alcohols that evaporate into the capsule shells could cause the drug to precipitate [58].

### Optimization of SNEDDS Composition

Stable SNEDDS formulations depend on the quantity of oils, surfactants, and cosurfactants, as well as the proportions of these ingredients. These variables and droplet size affect the possibility of self-emulsification and the absorption of active ingredients [59]. The aforementioned ingredients may be combined to create SNEDDS, along with additional additives like anti-oxidants, viscosity enhancers, and other compounds to help with drug release [60-63]. The solubility of the medication in various kinds of oils and surfactants is routinely examined in order to choose the appropriate components for the system. Typically, ternary phase diagrams are used to pinpoint the area of a self-emulsifying system where the concentration of the chosen oil, surfactant, or cosurfactant is impacted by the fixing of the concentrations of the other two constituents. Visual inspection and particle size analysis following dispersion in an aqueous media can both be used to pinpoint this area of the nanoemulsion. A surfactant that is more capable to dissolve the oil has a larger nanoemulsion area [64–66]. All SNEDDS compositions are related to the emulsification process that results in spontaneous nano-emulsions with droplet sizes less than 200 nanometers following aqueous dispersion [67]. The emulsification region may be impacted by the active components under particular conditions. Date *et al*. [68] reported that cefpodoxime proxetil greatly reduced the emulsification zone in the ternary phase diagram. The Box-Benkhen design, simplex lattice design, full-factorial design, central composite design, and D-optimal design are just a few examples of statistical experimental designs that can be utilized to optimize SNEDDSs [69-73]. The Box-Behnken design (BBD) was utilized to build and optimize the composition of SNEDDS of polypeptide-K using Design-Expert Dx 9.0.3 software. The design was used to statistically optimize the independent variables, which included the concentration of the oil oleoyl polyoxyl-6 glycerides, X1, the surfactant Tween® 80, X2, and the co-surfactant, X3 (30-40% v/v), and to assess the main effects and interaction effects of these formulation ingredients on emulsion droplet size (y1), PDI (y2),% drug loading (y3),

and zet (y4). To show response surface design, all of these variables were controlled at three levels (+1, 0, and 1) in the Box-Behnkhen design [74]. This model does a good job of capturing the quadratic behavior of the components. The total number of runs required to implement this design is N = 2k (k 1) + C0, where k and C0 are the quantities of independent variables and central points, respectively [75,76]. Garg *et al*. developed polypeptide-k as a self-nanoemulsifying agent utilizing Box-Benkhen design optimization. Greater oil concentrations in this investigation enhanced size (Y1), whereas higher surfactant and co-surfactant concentrations decreased size (Y1). The drug loading (Y3) expanded along with the X1, X2, and X3 ratios. The negative zeta potential (Y4) values of increased oil concentrations (oleoyl polyoxyl-6 glycerides, X1) were also discovered [74]. The most popular reaction surface designs are central composites. These fractional factorial designs feature specific axial points and center points that allow for the estimation of curvature [77]. Panigrahi *et al*. improved bosentan-loaded SNEDDS using PEG 600, MCM (oil, X2), capmul®, and labrasol® (surfactants, X1), and MCM (oil, X2) (Cosolvent, X3). It was discovered that the increase in particle size (Y1) at medium to high surfactant concentrations only happens when the amount of oil is decreased. The particle size also increases with a gradient reduction in the amount of surfactant, which also results in a decrease in the emulsification time (Y2). Additionally, Y2 will be added to the amount of oil produced. The percentage of medication release (Y3) was high when there was less oil. However, the percentage of drug release (Y3) was lower and Y3 was lower on the gradient drop of surfactant amount when the surfactant amount was higher [78]. A triangular grid of runs known as the Simplex lattice design occupies the available space. The excipient components of each formula must add to one, hence the factor, space, and mixing are represented in this model by a regular simplex [79]. Lattice scoring is used to determine points. This design shows how to quickly detect mixture properties for a variety of elements, especially for mixtures with four or more constituents. In a full factorial design, the dependent variables are influenced by two or more independent variables that interact with one another on several levels. For early experimental work, the full-factorial design is frequently helpful, especially when there are fewer than four independent variables [80]. A D-optimal design is produced by a computer algorithm. They are only employed when conventional experimental designs are insufficient. This class does not include orthogonal matrices [81]. Without altering the underlying mathematical model, this type can be used. It is a simple response design; the surface is based on the model that fits the data the best and according to the selected optimality criterion [82,83]. The key benefits of these statistical designs over ternary phase diagrams are the reductions in time, money, and labor. The characteristics of the self-nanoemulsifying system, including the droplet size, PDI, and time of emulsification, as well as the concurrent influence of oil, surfactant, and cosolvent, can all be measured.

## Supersaturable Self-Emulsifying Drug Delivery System

When a drug load surpasses its equilibrium solubility in a particular media, a supersaturation is the result. Supersaturable SNEDDS have been created to address a number of problems with conventional SEDDS. By substituting polymer for some of the surfactants or reducing the overall volume of the recipe, the amount of surfactant utilized in the finished product can be decreased. This can preserve the fast dissolving rate and oral bioavailability of SNEDDS while preventing potential surfactant adverse effects including GIT irritation [84]. This tactic is justified by the idea that increasing the drug's gradient of concentration at the absorption site acts as a catalyst for increasing the drug flux across the GIT epithelium, which enhances passive diffusion [85]. In the supersaturated aqueous solution, the drug molecules are thermodynamically unstable and tend to precipitate to attain the equilibrium condition. It is challenging to maintain a metastable condition in vivo for long enough for oral medication absorption at a high drug concentration that is greater than the saturation solubility concentration [86]. Mathews and Sugano suggest using a spring archlute to create the supersaturation preparation and then preserve it [87]. Due to its high solvent capacity, the SNEDDS formulation acts as a spring when applied to this procedure. This lays the groundwork for increasing the solubility of the medications to a supersaturated level. On the other hand, under in vivo conditions, a supersaturated preparation may exhibit drug precipitation, which may be brought on by dilution or a shift in pH [88]. Because of this, it's crucial to include a suitable precipitation inhibitor, which forms a parachute on the drug molecules' surface when they are supersaturated. As a result, the concentration of the drug will gradually rise until it reaches saturation solubility. Drug sedimentation, nucleation, and crystal formation are therefore constrained in a prolonged metastable parachute state [89].

## Drug Precipitation Inhibitor

Numerous excipients, such as surfactants (block copolymers like pluronic and soluplus graft copolymers), cyclodextrin, and polymers, have been investigated to stabilize the supersaturation condition (cellulosic polymer, vinyl polymer, and high molecular weight polyethylene glycol). Precipitation inhibitor type and dosage greatly depend on formulation [86]. To avoid medication precipitation, the degree of supersaturation can be decreased (thermodynamically) or the formulation-dependent drug precipitation might be postponed (kinetically) [87].

## Mechanisms of Precipitation Inhibition

Nucleation and crystal formation are the two sequential stages that typically lead to drug precipitation. The establishment of hydrogen bonds, interactions between molecules based on their molecular weight and hydrophobicity, and steric hindrance were all shown to be the basic methods by which most polymers can adsorb onto surfaces or interact with molecules to stop the medication from precipitating. While it is less crucial to increase the medium's viscosity or alter the level of solvation at the crystal and liquid contacts, certain polymers can make medications more soluble [90]. Lubna and Ahmed effectively optimized a novel liquid nebivilol-loaded supersaturable SNEDD formulation by using a liquid-solid strategy. The formulation contains Imwitor 988, cremophor EL, propylene glycol, and soluplus, which have been adsorbed onto a mixture of Avicel PH101 and Aerosil 200 [91]. Yeom et al. created a supersaturable valsartan-loaded self-microemulsion [92] to reduce the overall dose given. They found that when combined with an aqueous media, amphiphilic polymers, such as poloxamer 407 and tocophyrel propylene glycol succinate, are more successful at preventing drug precipitation than hydrophilic polymers. These polymers serve as precipitation inhibitors and surfactants. They increase the solvent capacity of SMEDDS for the drug and stabilize the micelle structure by mixing the amphiphilic polymers with the pre-existing surfactant for SMEDD formulation [92]. To increase the oral bioavailability of indirubin, Chen and colleagues developed supersaturable SEDDS [93]. They found that PVP K17 outperformed the two hydrophilic polymers tested, PEG4000 and HPMC, as a precipitation inhibitor. Additionally, they came to the conclusion that a low PVP concentration may support a high indirubin concentration while effectively preventing drug precipitation for up to two hours. Infrared spectroscopy and other analytical techniques revealed that hydrogen bonding and indirubin association within high-viscosity network topologies were responsible for the drug's delayed aggregation and crystallization. Supersaturable SEDDS released medications more fast than SMEDDS, according to an in-vitro release test [93].

## Solid Self Nano Emulsifying Drug Delivery System

The most popular commercial manufacturing method for SNEDDS is the formulation as a liquid that is put into a hard or soft gelatin capsule for solidification. This method comes with a number of drawbacks, such as the potential for some volatile components to interact with the capsule shell and shorten the product's shelf life and solubility in the formulation. The potential for liquid leakage if the capsules are not securely sealed and the requirement for specialist machinery to create the soft gelatin capsule, which increases the cost of production, are additional difficulties. Therefore, alternative methods will be required to circumvent these limitations while preserving all of the advantages and attributes of the liquid. In addition to economic considerations like packing, distribution, and storage, various techniques have been used to solidify liquid SEDDS and to create a variety of solid dosage forms, such as dry emulsion, capsules, pellets, or tablets, which provide additional advantages like improved stability and reproducibility. Numerous patents based on solid-state SEDDS have recently been granted, including those on carbon nanotubes, self-emulsifying osmotic pumps, and self-emulsifying gastro-retentive systems [89]. These innovative techniques will contribute to the development of SEDDS products in the future that are suitable for a variety of administration routes.

## Preparation of Solid-SNEDDS

Either directly, in a single process, or indirectly, by changing liquid-SEDDS into solid powder, SNEDDS can be prepared in their solid state [95]. The type and quantity of oily excipients utilized in the formulation as well as the therapeutic ingredient's physicochemical properties, such as its solubility, heat sensitivity, and compatibility with other excipients, all affect the technique choice [96]. A few techniques used to change liquid SEDDS into solid SEDDS are described below:

### *Melt granulation*

Since they give thermoplastic excipients their properties, this approach depends on using lipid-based excipients as a binder. Before becoming granules or pellets, the powder mixture is blended with a meltable binder in a high-shear mixer. Both the "pump-on" and "melt-in" techniques can be used to add binder. The process is similar to wet granulation with the exception of skipping the drying stage [97]. The melt granulation procedure is influenced by a number of variables, including the mixing rotation's speed and length as well as the particle size, concentration, and viscosity of the binder [95]. In melt granulation, self-emulsifying lipids such lecithin, partial glycerides, polyoxylglycerides (Gelucires®), and poloxamers can be utilized. Using melt granulation, the semisolid self-emulsifying lipid can also be incorporated into an inert solid carrier (such as silica or magnesium aluminosilicate) [98].

### *Melt Extrusion/Extrusion Spheronization*

Melt extrusion is a solvent-free procedure in which a substance with plasticizing qualities is pressed through a die. Hot-melt extruders have recently been used to produce solid SEDDS. Several factors, including temperature, flow rate, and recirculation time, need to be adjusted in order to achieve sufficient drug loading and adequate content homogeneity (especially for low-dose drugs) [99]. In the first stage of the multi-stage extrusion spheronization procedure, the liquid SEDDS are mixed with inert solid carriers to create a wet combination mass. The resulting extrudates are subsequently shaped into rod-like extrudates. The required size distribution is then achieved

by further chopping these extrudates into homogenous spheroids, drying them, and sieving them [40].

### *Spray Drying/Freeze drying/Rotary Evaporation*

The SNEDDS are disseminated in water containing a suitable carrier, such as mannitol, Aerosil 200, or lactose, while being continuously agitated, to produce a fine O/W emulsion. Drying methods for the finished emulsion include freeze-drying, rotary evaporation, and spray-drying [99]. Yan et al. produced liquid curcumin-SEDDS including lauroglycol Fcc, labrasol, and transcutol HP as oils, surfactants, and co-surfactants, respectively, to solidify curcumin-SEDDS using the spray drying technique [100]. After the aqueous phase evaporated, it was atomized to create liquid droplets in a spray dryer's drying chamber with controlled airflow and temperature, yielding dry powder. The outcomes demonstrated that the droplet sizes of the liquid and solid forms of SEDDS were equal. The resulting solid curcumin SEDDS formula displayed speedy and full dissolution within 5 min in both 0.1N HCl and phosphate buffer pH 6.8 dissolving medium [100]. For solidification, the lornoxicam formulation of Li *et al*. also used freeze-drying [101].

### *Adsorption onto solid support*

Among the several solidification technologies, the adsorption technique is the one that has attracted the most study attention since it is a simple and effective way to produce solid SEDDS. It includes employing a mortar and pestle or, for laboratory-scale applications, a mixer to combine the liquid formulation with the adsorbent carrier [95]. By choosing the optimum solid carrier with the capacity to absorb liquid SEDDS, high drug loading can be achieved. The efficient carrier must have high porosity and a sizable specific area in order to absorb or adsorb a sizable quantity of liquid SNEDDS [102]. A number of solid carriers have been studied as a result, including colloidal silicon dioxide, different grades of magnesium aluminometasilicate, dibasic calcium phosphate, calcium silicate, amorphous silica gel, microcrystalline cellulose, magnesium oxide, maltodextrin, and spray-dried lactose [95]. It's likely that the solidification process will clog the carrier's pores, preventing the medicine from being released. The kind and properties of lipids and carriers must therefore be taken into account when creating solid-state SEDDS since they may interfere with drug release [103].

### Limitation of SNEDDS

Drugs that display low solubility in water and lipids, as well as those that are delivered at very high doses, are not appropriate for SNEDDS [104]. If the surfactant or co-surfactant contributed more to the solubilization of the drug, the risk of precipitation would rise [105]. Lack of reliable predictive in vitro models for formulation evaluation due to the ineffectiveness of classic dissolve

techniques in formulations that may require digestion before drug release [106].

### Conclusion

For medicines with poor water solubility and BCS classes II and IV, SNEDDS is a potential strategy. The emulsification in SNEDDS allows for faster absorption and dissolution rates for medicines that are lipophilic. SNRDDS, which have been demonstrated to significantly increase oral bioavailability, can enable the oral distribution of hydrophobic medicines. The technology behind SNEDDS will continue to advance, enabling new drug delivery applications and resolving issues with the distribution of poorly soluble medicines.

### Conflict of interests

The author declares no conflict of interests.

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N/A

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