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Review Article

SNEDDS AS LIPID-BASED NANOCARRIER SYSTEMS: CONCEPTS AND FORMULATION INSIGHTS

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ABSTRACT

Approximately 40 % of newly discovered chemical entities have low solubility and possess low bioavailability after oral administration. Lipid-based drug delivery systems (LBDDS) have recently become very popular because of their remarkable ability to deliver drugs with poor absorption using lipids as carriers. Self-emulsifying drug delivery (SEDDS) systems are one type of LBDDS employed for the incorporation of hydrophobic drugs. SEDDS are classified into self-micro emulsifying drug delivery systems (SMEDDS) and self-nano emulsifying drug delivery systems (SNEDDS) based on the droplet size of the dispersed phase. The present review focus on the mechanism of drug absorption from lipid-based nanocarriers systems, *in vitro* assessment of self-emulsification, insights of SNEDDS, factors affecting the formulation of SNEDDS, and its applications.

Keywords: *In vitro* assessment of self-emulsification, Lipid-based drug delivery systems (LBDDS), Low bioavailability, Low solubility, Self-emulsifying drug delivery systems (SEDDS)

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INTRODUCTION

The oral route is commonly used for drug delivery because of its safety [1], comfort [2], minimum effort [3], and greater patient compliance [4]. However, many drugs have difficulty in developing as oral dosage forms because of their low solubility, low permeability [6], poor bioavailability, delayed onset of action, high inter/intra subject variability [5], and lack of dose linearity [6]. Different parameters, such as aqueous solubility, and rate of dissolution, influence the oral bioavailability of drugs. Susceptibility to efflux mechanisms, first-pass metabolism, and systemic metabolism has all been aspects to consider [7].

Combinatorial chemistry and high throughput screening (*in vitro* approaches) are used to identify the potent molecules in drug discovery process [8]. In the pharmaceutical research, more than 40% of NCEs (new chemical entities) are practically insoluble in water. Hence many of these promising active compounds are not considered in clinical-stage development [6]. Solubility of the drug is one of the major parameter to achieve the desired drug concentration in systemic circulation to produce therapeutic activity when administered [9]. The drug dissolution and gastro-intestinal permeability are the fundamental properties controlling the rate and extent of drug absorption [8]. Based on these properties, the biopharmaceutical classification system (BCS) classifies the drugs into four categories: Class I. High solubility-high permeability [2]; Class II. Low solubility-high permeability [3]; Class III. High solubility-low permeability [4]; Class IV. Low solubility low permeability [10]. Since many of the drugs belong to BCS II and IV their solubility and permeability problems are addressed by using conventional and novel techniques [11].

The conventional techniques are salt forms, solid dispersions [16], use of co-solvents [12], hydrotropy, micronization, change in dielectric constant of solvent, amorphous forms [7], chemical modification of drug, use of surfactants, inclusion complex [3], alteration of pH of solvent, use of hydrates or solvates [6], use of soluble prodrugs [8], application of ultrasonic waves [9], functional polymer technology, controlled precipitation technology [12], evaporative precipitation in aqueous solution [18], use of precipitation inhibitors, solvent deposition [4], precipitation [2], selective adsorption on insoluble carriers [9]. However, conventional approaches have many limitations like for example salt formation [12] of drugs is commonly used but always unattainable. Therefore weak acid and weak base synthesis are not practical [13]. Moreover, the formed salts might be converted into their original form [14], and it may cause the assembling of a weak acid and weak base in the gastrointestinal tract [4]. Reducing particle size might not be advisable because some of the processing problems may arise for amorphous powders [15]. In this direction novel techniques are developed to overcome the problems associated with conventional techniques. These includes lipid-based formulation system, micellar systems, porous micro particle, and nanoparticle technologies developed by using various polymers [14].

From the last decade onwards, lipids are used as carriers to modify solubility and permeability characteristics of drugs and is gaining attention [17].

Fats and oils are two common terms for lipids. At room temperature, fats are solid, while oils are liquid. Lipids [oils, greases, fats, and fatty acids (FAs)] are a key component of many natural foods as well as synthetic substances and emulsions. Various lipids that are employed to make lipid nanocarriers are biodegradable and show biocompatibility in physiological media or biological fluids [14]. Lipid based formulations are developed by dissolving the drug in mixture of two or more lipids.

To date, several studies have focused on lipid-based formulations for increasing the solubility and permeability of BCS II and class IV drugs by oral administration [15]. The present review focuses on the mechanism of drug absorption from lipid-based nanocarriers systems, *in vitro* assessment of self-emulsification, an overview of SNEDDS, factors affecting the formulation of SNEDDS, formulation insights, and its biopharmaceutical applications.

Introduction to lipid-based nanocarriers

Lipid-based nanocarriers

The term "nano" was derived from the Greek word that refers to microscopic dimensions beyond the naked eye's ability to see [12]. Nanocarriers are important transport agents because of their small size and capacity to change physical properties like charge and shape to transfer therapeutically active agents to tissues [15]. Nanocarriers provide several advantages, such as preventing active drugs from degrading, allowing for higher and more efficient concentrations in the target tissue, and reducing the severity of toxic side effects [16]. The lipid-based nanocarriers have greater importance due to their low toxicity [17], high drug-loading capacity [18], improved bioavailability [19], high biocompatibility [20], high protection from degradation in the gastrointestinal tract (GIT [21], controlled-release behavior [3], ease to scale-up and sterilize [6], easy to validate [2], and also useful for the administration of drugs through different routes [17]. Unique properties like, tailorable

surface to apply any targeting strategy, and an improved bio distribution and pharmacokinetic profile makes lipid-based system as a unique approach. Lipid nanocarriers are developed by using various types of biodegradable and biocompatible materials [20].

Lipid-based nanocarriers with complex nanostructures in the matrix can be made by properly blending solid lipids with liquid oil [7]. These systems are good at immobilizing substances and keeping particles from aggregating beneath the solid matrix [17].

Classification of lipid-based nanocarriers

Based on the physical state, lipid-based nanocarriers are classified as self-emulsifying drug delivery systems(SEDDS) [23], vesicular approaches, and non-vesicular approaches [19]. The sub classification of the same depicted in fig. 1. [14]. When introduced into the aqueous fluids of the gastrointestinal tract (GIT), SEDDS undergo emulsification and produce oil-in-water or water-in-oil emulsions [22]. Vesicular systems consists of a mixture of phospholipids, polymeric materials, and solvents [21]. One or more concentric bilayers are formed by self-assembling of amphiphile [19]. The drug is enclosed in between the phosphor-lipid bilayer. Non-vesicular systems are colloidal preparations containing physiological lipids and surfactants in which the drug in encapsulated within the solid lipid matrix [18]. Table 1 illustrates the difference between the various types of lipid-based nanocarriers.

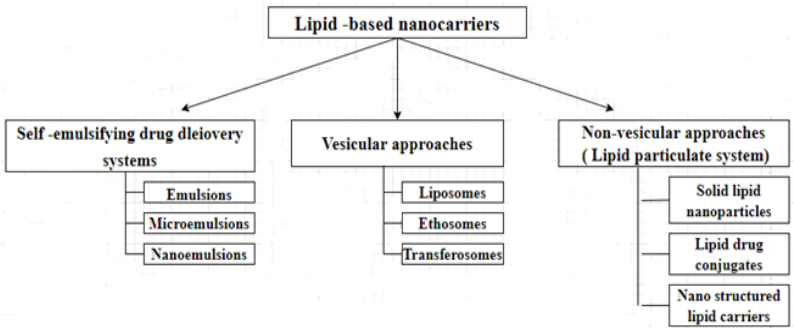
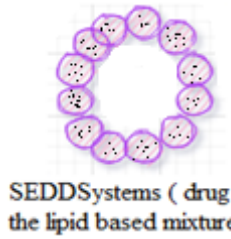
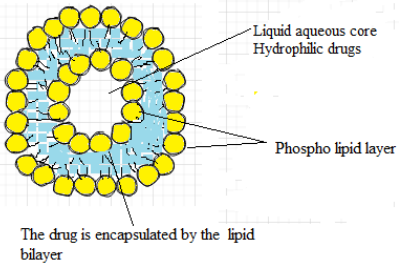
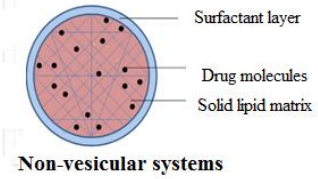


Fig. 1: Demonstrates the classification of lipid-based nanocarriers in detail [18]

Table 1: Differences among the various lipid-based nanocarriers

SEDDS	Vesicular systems	Non-vesicular systems	References
Contains a mixture of oils, surfactants, solvents, and co-solvents.	Contain a mixture of phospholipids, polymeric materials, and solvents.	Composed of lipids and surfactants.	[14]
Undergoes self-emulsification in presence of aqueous fluids.	Phospholipids completely cover the aqueous core.	Dispersion of lipids in an aqueous surfactant solution.	[24]
 SEDDSystems (drug is enclosed in the lipid based mixture)	 Vesicular systems	 Non-vesicular systems	

Mechanism of drug absorption from lipid-based nanocarrier systems

In the GIT, various enzymes (gastric lipase and pancreatic lipase) and intestinal components like phospholipids, proteins, polysaccharides, and amphiphilic materials are present [17]. Lipid formulations undergo emulsification in the GIT after its oral administration [19]. Gastric motility, gastric emptying speed, intestinal components and various enzymes play a major role in the emulsification of lipids [10]. Triglycerides undergo hydrolysis by gastric lipase and produce diglycerides and free fatty acids(FFAs) and then further undergo degradation by pancreatic lipase and form complex structures like mixed micelles [12]. The formed complexes are not absorbed completely. These complexes help to enhance the absorption of lipophilic moieties into enterocytes by passive diffusion [25] or by protein carriers placed on the membrane's outer surface [6]. Lipids helps in overcoming the first pass metabolism of the drug there by enhancing its gastric emptying time in the GIT and prolonging its residence time in the small intestine [1, 26]. Finally, lipids lead to better dissolution and enhanced drug absorption. Generally, lipid systems contain unsaturated long-chained fatty acid esters [3]. These ester groups undergo hydrolysis and enhances the bioavailability of the drugs [27], and thereby cause lymphatic transport [2].

Lipid-based formulations (LBFs)

Lipid based formulations are developed by dissolved and encapsulated the drug in the mixture of oil, surfactants, and co-surfactants [1]. LBFs helps to enhance the solubility and bioavailability of poorly water-soluble drugs; suitable for both liquid and solid dosage forms while protecting the drug from the gut. Also, these systems ensure high drug loading capacity [26]. Among the LBFs, self-emulsifying drug delivery systems(SEDDSs) have gained great attention [12].

Lipid-based formulation classification system (LBFCS)

Pouton and Porter introduced the lipid classification system [6] based on the type and amount of excipients [1] used and by considering the morphology of lipid aggregates [3]. This classification helps in the selection of lipids based on their properties in formulation development [20]. As per their classification, the LBFCS are divided into four types. In Type I

systems drug is incorporated in a single or mixture of triglycerides and excluding the surfactant [25]. These systems are easily digested and absorbed completely on administration [12] and are suitable for highly lipophilic drugs whose log P-value is greater than 4 [1].

In type II formulations, oil and water-insoluble surfactants are used [15] in contrast to water-soluble surfactants [12], which undergo self-emulsification when they come in contact aqueous medium [20]. Type III A and Type III B formulations uses oils, surfactants, and co-solvents [19]. Type IV formulations use water-soluble emulsifiers and co-solvents(propylene glycol and ethanol) to enhance drug solubilization by undergoing drug colloidal dispersion [25]. Table 2 illustrates the different types of LBDCS in terms of its features and composition aspects.

Table 2: Lipid-based formulation classification system

Formulation type	Identifying features	Composition	Digestion's influence	Precipitation risk, i.e., loss of solvent ability during dilution/digestion
Type I	Pure oils [20]	Oils [30]	Digestion required [5]	No loss of solvent capacity
Type II [6]	SEDDS (HLB<12) [23]	Oils: surfactants 4:1-1: 1.5 [16]	Likely to require [31] digestion	Minimum loss of solvent capacity
Type III A [12]	SMEDDS(HLB>12) [3]	Oils: surfactants 4:1-1:1, cosolvents<40% [8]	May require digestion [16]	Moderate loss of solvent capacity
Type III B [23]	SNEDDS (HLB>12) [20]	Oils: surfactants 4:1, cosolvents 20%-50% [2]	Digestion may not be necessary [10].	Moderate loss of solvent capacity
Type IV [17]	Oil-free (HLB>14) [18]	Surfactants: co-solvent 4: 1-1:1 [1]	Digestion independent [12]	The maximum loss of solvent capacity

The most prominent and widely accepted formulation approachto incorporate the drugis self-emulsifying drug delivery systems (SEDDS).

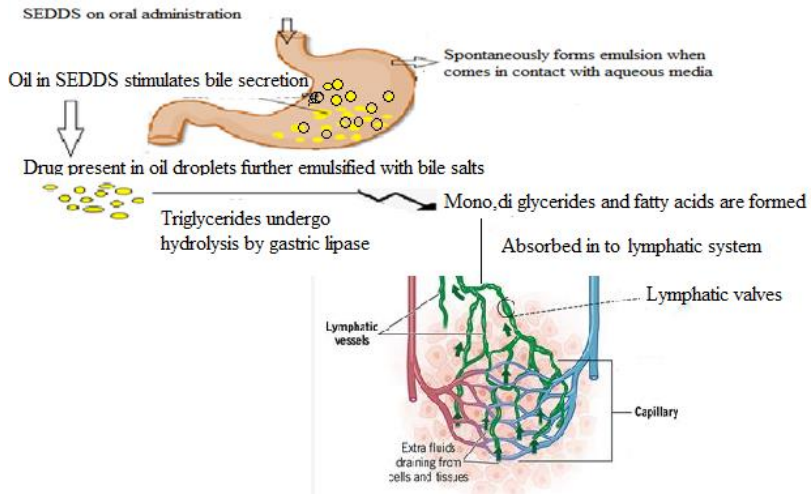


Fig. 2: Process of self-emulsification

Process of self-emulsification

When an isotropic mixture [1] of oils [3], surfactants [29], co-surfactants [16], and co-solvents is introduced into the alimentary canal (GIT), an immediate emulsification process occurs [26]and it is known as self-emulsification [24]. The self-emulsification process in the GIT is shown pictorially in fig. 2.

***In vitro* assessment of self-emulsification**

When the SEDDS come in contact with aqueous medium with gentle agitation, the energy is released [2]. The released entropy is larger than the required energy to extend the surface area between the system's immiscible phases [1]. The best method for assessing self-emulsifying ability is by dilution method with visual observation. Based on the system's physical appearance, they are grading as A to E, and fig. 3 depicts the distinct differences among the different types of systems [12].

Grade A: These systems rapidly form as nanoemulsions within one minute. These are clear and slightly dark blue colored in appearance.

Grade B: These systems form rapidly as emulsions but appear turbid with dark-blue to white color.

Grade C: These systems form within two minutes and look like a milky emulsion.

Grade D: Emulsions are formed gradually, and the formed emulsion appears to be grayish-white and has a slightly oily appearance.

Grade E: These systems have poor emulsification properties, and large oil globules are present on the emulsion surface.

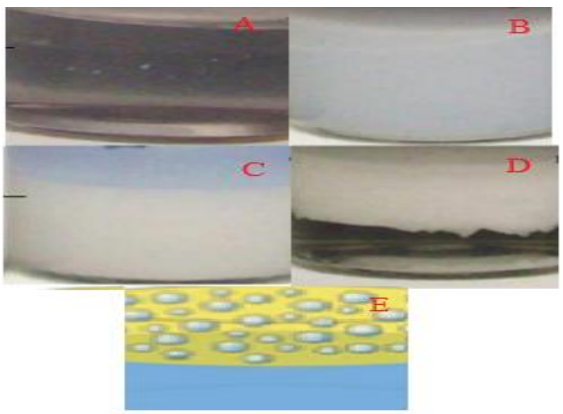


Fig. 3: Assessment of self-emulsification by visual method

Note

Grade A: Transparent or slightly dark-blue look, Grade B: Slightly white look,

Grade C: Fine milk-like emulsion, Grade D: Grayish white emulsion with slightly oily look and

Grade E: Minimal emulsification with large oil globules present on the surface.

The visual method helps to observe the emulsification speed and emulsion's stability with varied periods [33].

Self-emulsifying drug delivery systems (SEDDS)

These systems are lipid-based systems containing homogenous mixtures of oils, surfactants, and co-solvents [24]. Generally, these are anhydrous and are known as preconcentrates [34]. Under gentle agitation in an aqueous phase, the SEDDS has undergone self-emulsification spontaneously to form o/w microemulsions or nanoemulsions with an average particle size of 200 nm or less [24]. Fig. 4 shows the graphical representation of SEDDS prepared under gentle agitation employing a magnetic stirrer.

Types of SEDDS

Based on the droplet size SEDDS are categorized into two types [1]: A) self-micro emulsifying drug delivery systems (SMEDDS) [34], B) self-nano emulsifying drug delivery systems (SNEDDS) [16]. SEDDS refers to all forms of self-emulsifying systems [2], containing a mixture of oils, surfactants, and co-solvents (or) co-surfactants [25]. When the mixture of SMEDDS come in contact with the aqueous environment in GIT, they form a microemulsion under gentle agitation provided by the digestive motility of the stomach and intestine [34]. At the same time, SNEDDS refers to systems that generate nanoemulsions when dispersed in aqueous media [16]. The differences between SEDDS, SMEDDS and SNEDDS systems are given in table 3.

Fig. 4: SEDDS preparation using a magnetic stirrer

Table 3: Differences between SEDDS, SMEDDS, and SNEDDS

Self-emulsifying drug delivery systems [23]	Self-micro emulsifying drug delivery systems [34]	Self-nano emulsifying drug delivery systems [30]
Oil droplet size ranges from 200 nm-5 µm [10]	Oil droplet size is 100-250 nm [32].	Oil droplet size is <100 nm [29].
Appearance is turbid	Appearance is optically clear to translucent	Optically clear appearance
Required HLB value is < 12	Required HLB value is > 12	Required HLB value is > 12
Development may require the characterization of the ternary phase diagram [23].	Development may require the characterization of pseudo ternary phase diagrams [10].	Development may require the characterization of pseudo ternary phase diagrams.
A ternary phase diagram shows possible phases and equilibrium according to the composition of a mixture of three components at constant temperature and pressure.	Construction of pseudo ternary phase diagram is a critical step for developing SMEDDS/SNEDDS lipid-based formulation [16], which self-disperses as thermodynamically stable nano-drug carrier in GI lumen. It will provide information on phase behavior between different formulation components.	

What are SNEDDS?

Self–nano emulsifying [12] drug delivery systems (SNEDDS) are nanoemulsion preconcentrates [10] or anhydrous sorts of nano-emulsion [25]. These systems are homogenous isotropic mixtures [16] of a pharmaceutical component, either natural or synthetic lipids, surface-active agents (surfactants), co-surfactants, and co-solvents [12]. When the mixture of these components undergoes gentle agitation in an aqueous solution, like GI fluids, it immediately forms an o/w nanoemulsion in which the drug is encapsulated [16]. Fig. 5 summarizes the process of self-nano emulsification.

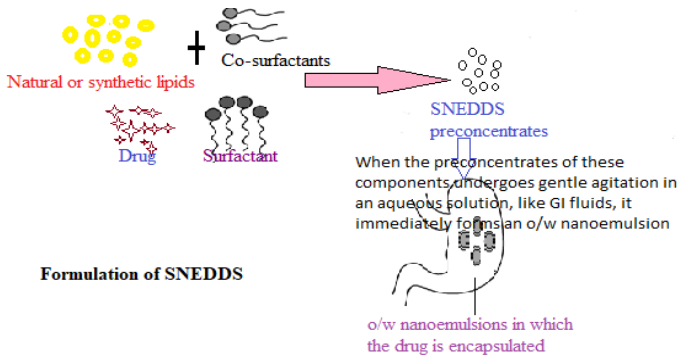


Fig. 5: Formulation of SNEDDS [35]

Advantages of SNEDDS

Based on the composition and formulation, SNEDDS offer some advantages when compared to other lipid-based formulations:

- Upon long-term storage, physical/chemical stability is not effected [25].
- Possibility of filling them into unit dosage forms, like soft/hardgelatin capsules [10].
- Improves their commercial viability [25] and patient compliance/acceptability [29].
- No palatability-related issues [10].

- Ability to carry the drug in liquid forms, all through the GIT, for adequate time and permits its absorption [25].

Factors affecting the formulation of SNEDDS

Generally, SNEDDS has been formulated as a combination of oils, surfactants, and co-surfactants or co-solvents; based on their properties, various factors affect the formulation of SNEDDS.

- Drugs administered at a very high dose are not suitable for SNEDDS unless they exhibit extremely good solubility in at least one of the components of SNEDDS, preferably the lipophilic phase. The drugs with limited solubility in water, and lipids are most difficult to formulate by SNEDDS [30].

- The ability of SNEDDS to maintain the drug in solubilized form is greatly influenced by its solubility in the oily phase [5]. Suppose if the surfactant or co-surfactant is contributing to a greater extent in drug solubilization, there could be a risk of precipitation, as dilution of SNEDDS will lower the solvent capacity of surfactant or co-surfactant [16].

Formulation considerations

In the selection of formulation ingredients care must be taken. Preformulation experiments (e. g., solubility, emulsification efficiency) should be conducted in order to choose the best constituents for SNEDD formulation.

The variables factors affecting the phenomenon of self-nano emulsification are:

- The physicochemical nature and convergence of oil phase, surfactant, and emulsifier [36].

- The proportion of the mixture, particularly oil-to-surfactant [12].

- The temperature and pHof the aqueous phase where nano emulsification would happen [25].

- Physicochemical properties of the API, for example, hydrophilicity/lipophilicity and pKa [10].

- Physicochemical properties of the selected oily, surfactant, and emulsifier and their concentration [29]**.** The formulated droplet size and its polar nature can regulate the coherent release of the core from the system [10]. The routes of administration also play a major role in selecting the formulation ingredients and their ratios [31].

The general components used in the development of SNEDDSs are listed below.

Drug molecule

It is important to remember that the therapeutic agent can impact SNEDDS in various ways, including phase behavior and nanoemulsion droplet size [10]. The efficiency of SNEDDS is affected by various physicochemical properties of the compound, including log P, pKa, molecular structure and weight, the existence of ionizable groups, and quantity [12].

Potential components

Excipients used in the formulation of SNEDDS have been developed due to advances in pharmaceutical science w. r. t solubility, safety and toxicity [29]. When selecting appropriate excipients, consider irritation potential, safety for administration into the body [10]. A perfect oil, surfactant, and co-surfactant ratio contributes to stable and efficient SNEDDS [30]. The length of the fatty acid carbon chain and degree of unsaturation of the selected oil and surfactant will greatly determine the formed emulsion's stability [30]. The various components used are as follows:

Oils

The oil phase is necessary to formulate SNEDDS because oil's physicochemical properties regulate the nano-emulsification process's spontaneity [31]. Oils with excessively long hydrocarbon chains, such as fixed oils, are considered difficult for nanoemulsions [23]. In contrast to medium-chain, tri-, di-, and mono-glycerides(examples are glycerol mono caprylocaprate, acetic, citric, diacetyl tartaric acids), long-chain triglycerides have shown a greater capacity to enhance intestinal lymphatic transport of drugsas these are reported to be responsible for preventing the first-pass metabolism of drugs [12], while medium-chain mono-and diglycerides have greater solubilization potential for hydrophobic drugs with permeation-enhancing properties [10]. When a single oily component have optimal nano emulsification and drug delivery properties, a combination of oils could be used to achieve a good oily phase property [30]. Nanoemulsions and microemulsions are generally made using a similar concept by using a combination of oils to have high solubility for the added drug.

A mixture of fixed oil and medium-chain triglyceride are used in some situations to maintain a good balance between drug loading and emulsification. SNEDDS containing lacidipine [10], a calcium-channel blocker with poor oral bioavailability, has recently been produced using a mixture of oils(based on a three-component system: the oil phase X1 (a mixture of Labrafil®/Capmul®, 2:1, w/w), the surfactant X2 (a mixture of Cremophor®/Tween® 80, 1:1, w/w) and the co-surfactant X3 (Transcutol®)) and the authors reported high solubility of the drug in the selected components [38].

Surfactants

Surfactants, known as surface-active agents, are amphiphilic compounds containing polar (water-soluble) and non-polar (water-insoluble) groups. Surfactants adsorb at interfaces due to their amphiphilic nature, decreasing surface and interfacial tension and leads to emulsification. Khan *et al.* developed naringenin SNEDDS by proper selection of surfactant and co-surfactants, thereby enhancing the drugs solubility [38].

Emulsification results have shown that many surfactants have different emulsification abilities [25]. A proper mixture of low and high hydrophilic lipophilic balance (HLB) surfactants is needed to develop a stable self-nano emulsifying system [1]. A sufficient ratio of surfactants with an HLB value of 14–16 helps in the most effective emulsification when diluted with water [16]. A high HLB surfactant does have the advantage of increasing interfacial fluidity and emulsification of SNEDDS [39].

Co-emulsifiers, co-surfactants, or solubilizers

Co-emulsifiers [10], co-surfactants [40], or solubilizers [16] are widely used in the formulation of SNEDDS [30]. These are included during the formulation for various reasons, such as in increasing the drug loading [10], controlling the self-nano emulsification time, regulating the size of nanoemulsion droplets [30], and increasing the size of the self-nano emulsification area in phase diagrams [29]. Solubilizers, for example, ethanol, propylene glycol, polyethylene glycol, and glycol ethers, are utilized to upgrade the disintegration of vast amounts of hydrophilic surfactants.

Aqueousphase

The formation of SNEDDS occurs when a combination of oils, surfactants, co-solvents, and drug molecules are added into the aqueous media [6]. The stomach's pH is usually acidic (pH 1.5 to 2.5), and various ions in the GITsignificantly impact nanoemulsions' properties in terms of their size and stability [25].

The various components, along with examples, are mentioned in table 4.

Advantages of snedds/ssnedds over micro/nanoemulsions

SNEDDS/SSNEDDS demonstrates many advantages when compared with micro/nanoemulsions. Some of the advantages are discussed below.

Stability

The stability assessment has done based on the droplet size, polydispersity index (PDI), and zeta potential (ZP) of SNEDDS [25]. When compared to nanoemulsions, SNEDDS have excellent physical and chemical stability during long-term storage [43].

Palatability

Compared to other formulations, these systems do not have palatability problems, even though they can be filled into capsules [12].

Table 4: Components of SNEDDS

Components	Examples
Lipids [6], oils [1] (Fatty acids [5]and Fatty acid esters [29])	Fatty acids: Palmitic acid [41], Stearic acid [13], Oleic acid [30]. Fatty acid esters: Glyceryl monooleate [42], Glyceryl monostearate, Glycerylmonolinoleate, Glyceryl palmitate stearate, Glyceryl behenate, Ascorbyl palmitate, Medium-chain mono-and diglycerides [25], Medium-chain triglycerides [26], Glyceryldilaurate, Propyleneglycolmonolaurate, Propylene glycol esters, Propylene glycol esters Propyleneglycolmonolcaprylate, Propylene glycol dicaprylocaprate [23]. **Oils** Corn oil, Sesame oil, Soya bean oil, Peanut oiland Hydrogenated soya bean oil [1].
Surfactants [23]/stabilizers [25]	Caprylocaproylpolyoxyl-8-glycerides, Tween20, Polyoxyethylene sorbitan fatty acid esters [25], Polyoxyethylene castor oil derivatives, Polyvinyl alcohol, Sorbitan esters, Tocopherol polyethylene glycol, succinate PGS),Macrogol fatty acid glycerides [20], Gelucire 44/14, Gelucire 50/13, Hydroxyl propyl methylcellulose, Poloxamer, Phospholipids, and PEGylated phospholipids, Polyvinyl pyrrolidone [11], Bile acids (sodium deoxycholate), Cellulose derivatives [10], Polyglyceryl-3 dioleate, Span 80, Tween 80, Cremophor RH 40, D-alpha Tocopheryl Polyethylene Glycol [31].
Co-surfactants [26]/co-solubilizers [25]	Propylene glycol [12], Glycofurol [16], Phospholipids [8], Oleoyl/linoleoyl polyoxyl-6-glycerides [29], Polyethylene glycol [24], Triacetin, Ethanol [25], Diethylene glycol monoethyl ether, glycerine [20], and ethanol.
Miscellaneous [31]	Stearyl alcohol, Phospholipids, Bees Wax, Vitamin E [20]

Drug loading

As natural lipids have a lower solubility of compounds with intermediate partition coefficients (log P 1-3) than amphiphilic surfactants/co-surfactants [31], SNEDDS has a higher drug-loading capacity than lipids solution due to higher surfactant and co-surfactant concentrations and less oil [29]. As compared to those formulated with long-chain (LC) lipids, SNEDDS prepared with medium-chain (MC) lipids with Cremophor RH40 as a surfactant were able to dissolve more drugs. The high drug-loading capacity of commercial products like Fortovase®, which contains 200 mg of drug per capsule, is critical in their performance [23].

Quick onset of action

Quick action is required in various conditions, such as aggravation, hypertension, and angina [12]. SNEDDS can provide quick onset of action when administered *via* the oral route as it undergoes spontaneous emulsification in the gastrointestinal tract (GIT) [15]. In comparison to traditional formulations, pharmacokinetic studies of SNEDDS revealed a strong reduction in tmax (an indirect measure of the fast onset of action) in the case of SNEDDS [30].

Reduction in the drug dose

The SNEDDS has improved Cmax, oral bioavailability, and therapeutic effect [31]. Many hydrophobic pharmaceuticals (antihypertensive and anti-diabetic), improved the bioavailability when manufactured as SNEDDS with reduced drug dosage and dose-related side effects [12].

Simple manufacture and scale-up

Industrial applicability determines any drug delivery system's success. Simple manufacturing and scale-up are essential factors in industrialization's success [15]. SNEDDS requires basic and cost-effective manufacturing facilities [22], such as a simple mixer with an agitator and volumetric liquid filling equipment; they can be mass-produced easily and affordably [44].

SNEDDS can form acceptable o/w emulsions on mild agitation, dilution in media(GI fluids) [12]. SNEDDS overcomes the initial rate-limiting stage of particulate dissolution within the GI tract as the formulation is pre-dispersed in a suitable solvent [31]. The system can present the drug in a single unit dosage form with increased solubility while retaining dose uniformity [8].

Applications of snedds

When a drug is formulated as a SNEDDS, the dissolution process is bypassed, which increases the drug's solubility and bioavailability [22]. In SNEDDS, the lipid matrix readily combines with water to produce a fine particulate o/wemulsion [16]. The medication would be administered in a dissolved state to the GI mucosa, allowing it readily absorbable. The bioavailability and Cmax of several drugs, when present as SNEDDS, is increased [1].

Glyburide is an oral second-generation sulfonylurea medication employed throughout the treatment of type II diabetes. The addition of glyburide to SNEDDS improved the drug's solubility significantly [8].

The preparation of docetaxel-loaded SNEDDS by Y. G. Seoet al. resulted in a 6-fold increase in docetaxel bioavailability [45]. The significant increase in bioavailability showed that SNEDDS could improve drug absorption by inhibiting the(permeability glycoprotein)p-GP efflux mechanism [1].

Ziprasidone sustained-release pellets with SNEDDS were designed to increase oral bioavailability and overcome the drug's food impact [46]. From the drug release test it was found that the pellets provided sustained release, with 90% of the pellets being released within 10 h. Pharmacokinetic tests in beagle dogs revealed that ziprasidone had prolonged the action and improved bioavailability with no food impact. Findings showed that the effects of schizophrenia and bipolar depressive medication persisted for a long time [46].

SNEDDS is a method for increasing drug solubility that is independent of the pH effect on solubility. Cefpodoximeproxetil (CFP), a poorly bioavailable high-dose antibiotic with pH-dependent solubility, was developed into self-nano emulsifying drug delivery systems. Resulted SNEDDS have a greater release rate when compared with a pure CFP [47].

A similar technique was used to increase the oral bioavailability of the model protein beta-lactamase (BLM). The theory is that the amphiphile will encircle the protein and form a micelle structure within the oil, allowing it to dissolve more frequently. Cell line studies revealed that the SNEDDS significantly increased fluorescein isothiocyanate-beta-lactamase transport across the Madin-Darby Canine Kidney monolayers. (FITC-BLM transport across MDCK monolayers) [53].

SNEDDs could also be a possible effective delivery system for non-invasive protein drug delivery. Insulin was used as a model protein to support a complex between a hydrophilic moiety and a phospholipid. The insulin phospholipid complex (IPC SNEDDS) showed a strong ability to lower glucose levels in diabetic rats. The relative bioavailability reached 7.15 percent after oral administration, significantly higher than the 0.11 percent of MDCK cells monolayers-phosphate buffered saline (PBS) [48]. Table 5 enlist the SNEDD Sreported for the different routes of administration along with reports related to SSNEDDS.

Formulation of snedds

The formulation of SNEDDS pseudo-ternary phase diagrams plays a major role in selecting optimal oil concentrations, surfactant/co-surfactants, co-solvents needed to solubilize and stabilize the SNEDDS [28]. These systems are prepared on a simple vortex mixer. The drug's required amount is solubilized in the surfactant and co-surfactant mixture followed by oil addition. In general, soft/hard gelatin or hydroxypropyl methylcellulose capsules deliver liquid SNEDDS [16]. When filled into capsules, limitations were noticed and are as follows:

a) Component incompatibility with the capsule shell may occur during long storage [5].

b) Drug can precipitate during the manufacturing process and when stored at low temperatures [41].

c) A critical production method is needed compared to other conventional dosage forms [47].

d) SNEDDS may well not be effective for hydrophobic drugs that are subjected to pH-catalyzed or solution-state degradation during accelerated storage (hydrolytic degradation) [27, 50].

Table 5: SNEDDS as a nanocarrier for lipophilic drugs

S. No.	Routes of administration	Drug	Inference	References
1.	Oral Route/Parenteral Route	Cilostazol (CLZ)	Capryol 90, Cremophore EL, and Transcutol HP were used as the oil phase, surfactant, and co-surfactant in the SNEDDS preparations. A small droplet size provides a large interfacial surface area for drug absorption. The study has indicated that self-nano emulsifying drug delivery systems of the poorly water-soluble drug CLZ were successfully prepared and optimized. Oil phase, surfactant, and co-surfactant in the ratio of 19.8:30.5:49.7 was able to dissolve cilostazol 2000 times greater than its solubility in water.	[44]
2.	Transdermal Film	Saquinavir mesylate (SQR)	Clove oil, Labrasol, and Transcutol were used as oil, surfactant, and co-surfactant to formulate SQR SNEDDS. The formulated SNEDDS were made into transdermal films, and the loaded film werefound to have smallest globule size with high stability index. As compared to pure SQR-loaded film, SNEDDS loaded films had better folding endurance and tensile strength also.	[28]
3.	Oral Route	Chlorpromazine	The use of SNEDDS has resulted in a significant increase in the oral bioavailability of an extremely lipophilic drug because of long-chain fatty oils in the formulation.	[41]
4.	Vaginal route	Clotrimazole (CT)	Clotrimazole SNEDDS were developed using oleic acid with coconut oil, tween 20, and polyethylene glycol (PEG) as oil, surfactant, and cosurfactant. The prepared SNEDDS of CT produced acceptable properties in terms of droplet size, turbidity values, and immediate release that could increase CT's bioavailability when compared with commercial products.	[49]
5.	Ocular route	Lutein	SNEDDS of lutein were formulated with 53 MCT, Labrasol, and Transcutol-HP as an oil, surfactant, and cosurfactant. The final optimized formulation possessed good emulsification and immediate dissolution compared with lutein and with commercial product (Eyelac®).	[42]

Solid SNEDDS

To address the drawbacks of SNEDDS, researchers have contributed to converting liquid systems to solid SNEDDS (S-SNEDDS). The most stable dosage forms are solid dosage forms, which are also the easiest to handle. Spray drying, freeze-drying, and adsorption on carriers are standard methods for turning SNEDDS into solid SNEDDS. The proper selection of solid carriers is crucial for producing an effective formulation. HPMC E-type polymers, a commonly used polymer [16], have more adsorption properties and precipitation inhibitors. Ezetimibe SSNEDDS was formulated using HPMC E as anadsorbent. Mahmoud *et al.* prepared self-nano emulsifying carvedilol tablets. It demonstrated the effective incorporation of carvedilol within the SNEDDS, which enhanced its stability in the presence of cellulosic polymers when diluted with aqueous media [24].

Preparation of solid SNEDDS

Solid SNEDDS are typically prepared using any of the three methods.

I) Adsorption on a solid inert carrier [16].

II) Spray drying [27]

III) Extruder-Spheronization [46]

The liquid formulation is introduced to the carrier by mixing it in a blender during the adsorption process. The free-flowing powder is resulted [16]. Spray drying is a procedure for rapidly drying a liquid or slurry into a dry powder. The volatile fraction of the microemulsion, i.e., the organic solvent or water, is evaporated by spraying a liquid solution into a hot-air chamber. The basic machine consists of a spinning friction disc that spins at high speed at the bottom of a cylindrical pipe designed to maximize friction with the product [52]. In the Extruder-Spheronization method, the wet mass is passed through an extruder at 30 pm. The extrudates were then placed in a spheronizer fitted with a cross-hatched plate rotated at 1800 rpm for 15 min [11]. Table 6: shows some of the examples of S-SNEDDS by using three methods.

Table 6: Various carriers for the development of S-SNEDDS

S. No.	API	Excipients/ adsorbents	Method adopted for NEEDS	Inference	References
1.	Valsartan [16]	Porous carriers like Aerosil 200, Sylysia 350, 550, 730, and Neusilin US2	Adsorption on a solid inert carrier	Liquid SNEDDS are converted into S-SNEDDS by using porous carriers. The developed S-SNEDDS had a better drug release rate than conventional marketed preparation and pure drug. Based on the *in vitro* studies, the S-SNEDDS approach is suitable for enhancing the bioavailability of valsartan.	[16]
3.	Deferasirox [44](DFX)	Neusilin UFL2, Neusilin US2, and Syloid XDP 3150	Adsorption on a solid inert carrier	DFX loaded SNEDDS would be incorporated into S-SNEDDS formulation by adsorbing into different porous carriers to compare their dissolution behavior with the commercially available tablet formulation of DFX. To create and characterize a new DFX-S-SNEDDS to increase its solubility and possibly improve its oral bioavailability.	[43]
6.	Sertraline hydrochloride [27]	The hydrophilic solid carrier PVP or lactose	Spray drying	Liquid sneddsof sertraline HCl are converted into solid snedds by using the spray drying method. The developed solidsnedds have a fine particle size and show greater drug release bioavailability.	[27]
7.	Irbesartan (IRB) [52]	Aerosil 200 as solid carrier	spray drying technique	Liquid snedds are suspended in the solid carrier using ethanol as a solvent with continuous stirring until forming an isotropic mixture. The formed suspensions are spray dried. The formed s-snedds have oral bioavailability when compared with pure IRB.	[51]
8.	Loratadin [53]	Aerosil,Crosscarmellose	Extrusion-Spheronization	The developed Loratadin S-SNEDDS have a uniform size and spherical shape. These have improved drug release when compared with L-snedds.	[52]

Future perspective

From the last decade onwards, research on SNEDDS has increased, and various studies have appeared in the literature. For the enhancement of solubility and bioavailability of oral drugs SNEDDS have been developed. Based on the literature, SNEDDS are used to administer other than the oral route. The routes of drug distribution have been the focus of extensive research. The conversion of liquid SNEDDS to solid dosage forms like tablets and pellets has been extensive research. However, a suitable highly porous amphiphilic carrier that can change liquid SNEDDS into a solid powder without significant volume or bulk density increase is required. The drug is released for an extended period by incorporating polymers into SNEDDS. Even though there is much study being done in this field, the ability of drug delivery researchers to handle these issues of SNEDDS technology would be critical to its commercialization.

CONCLUSION

Many promising active compounds are not considered in clinical-stage development due to their low solubility and oral bioavailability. Solubility of the drug is one of the major parameters to achieve the desired drug concentration in systemic circulation to produce therapeutic activity when administered orally. Solubility of the NCMs (new chemical moieties) is one major challenge present in front of pharmaceutical researchers. From the last decade onwards, lipids have had much more interest as carriers to modify poorly water-soluble drugs' solubility and permeability characteristics. The development of lipid-based formulations in general and SNEDDS can increase poorly aqueous soluble drugs' solubility, stability, and bioavailability.

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All authors have contributed equally.

CONFLICT OF INTERESTS

Declare that there is no conflict of interest regarding the publication of this paper.

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