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Solid Self Nano Emulsifying Drug Delivery System (S-SNEDDS): A Technique to Enhancement of Bioavailability

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ABSTRACT

Most of the newly discovered drug moieties (around 40%) are poorly water-soluble, resulting in low bioavailability. Enteral delivery is the most convenient route of administration but it has several problems, to overcome problems associated with enteral delivery by formulating a Self-Nano-Emulsifying Drug Delivery System (SNEDDS). Solidification (conversion of liquid into solids) of SNEDDS make the formulation ease of handling, patient compliance, enhanced stability, precise dose administration of drug. The solidification process employs several solid carriers either natural or synthetic or combination of both polymers. Coffee husk powder is a naturally occurring, non-toxic, inert adsorbents it is used in conversion of liquid SNEDDS into Solid SNEDDS (S-SNEDDS). Drug solubility, release profiles and *in-vivo* characteristics are optimised by using appropriate excipients such as concentration of oils, ratio of oil and surfactant mixtures. Optimisation of the emerging strategy of SNEDDS formulation was done by statistical design and pseudo ternary phase diagram, solubility of drug in different oils and surfactants are determined by using pseudo ternary phase diagram, this diagram shows the region of self-emulsification. Characterisation of Solid SNEDDS reveals the type of emulsion, mean globule size, surface morphology, surface charge, drug release pattern and biological fate.

INTRODUCTION

Due to patient compliance and convenience of administration, enteral administration is the most recommended method. In comparison to intravenous infusion, enteral administration would have advantages such as patient appeal due to its simplicity and ability to facilitate the creation of treatment regimens that would result in sustained plasma concentrations beyond a threshold level that is relevant to pharmacology.[1] It frequently has low bioavailability because of either low drug permeability, water solubility, or drug dissolution rate. It frequently has low bioavailability because of either low drug permeability, water solubility, or drug dissolution rate. [2,3]

Roughly 40% of newly developed medications have low water solubility, which leads to low variable enteral bioavailability, high inter- and intra-subject variability, and lack of dose proportionality. [4] Class II drugs in the biopharmaceutical classification system frequently have low water solubility, which limits their enteral bioavailability. There are now several approaches available, but one of the main formulation techniques to solve poor bioavailability difficulties is the development of lipid-based drug delivery systems. By creating a lipophilic milieu and a concentration gradient that guide the flow of medications to the proper intestine absorptive sites, these delivery methods enhance the solubilization of active substances. [2,3] The lipid formulation classification system was created to provide the best possible formulation for a given medicine based on its qualities and to predict the drug's behaviour in vivo through a variety of research [5]. Several strategies can be used to increase bioavailability, including the use of prodrugs, surfactants, crystal polymorphism, salt formation, pulverization, particle size reduction, solid dispersion, microemulsion, liposomes, complex formation, nanoparticles, nano and microspheres, and permeation enhancers. [6,7] A combination of oils, surfactants, and cosurfactants or cosolvents has been referred to as SNEDDSs. After being dissolved in water and gently shaken (as in the gastrointestinal tract), SNEDDSs naturally create fine oil-in-water nano-emulsions with droplet sizes of 200 nm or less. [5,8] According to recent research, SNEDDSs may be useful enteral medication carriers for proteins and peptides because they enhance intestinal membrane permeability and inhibit GI breakdown. [9] This paper has adequate information about the SNEDDS such as components, formulation, characterization, and evaluation.

Advantage of SNEDDS [10]

- SNEDDS increase the drug's bioavailability, which lowers the frequency of dosages.
- Selective medication targeting to a specific GI tract absorption window is made possible by SNEDDS.
- Their medication payload is larger. The regulated medication delivery profile is managed by SNEDDS.
- SNEDDS are made with a very stable formulation and simple manufacturing methods.
- A greater surface interfacial area is made possible for drug partitioning between oil and water by SNEDDS.
- Wider medication distribution in the stomach and GI tract was made possible by SNEDDS, which also lessened the irritation that results from a drug's prolonged interaction with the gut walls.
- The medication is shielded from the harsh GI tract environment by SNEDDS.
- The pace and extent of absorption are enhanced by SNEDDS.

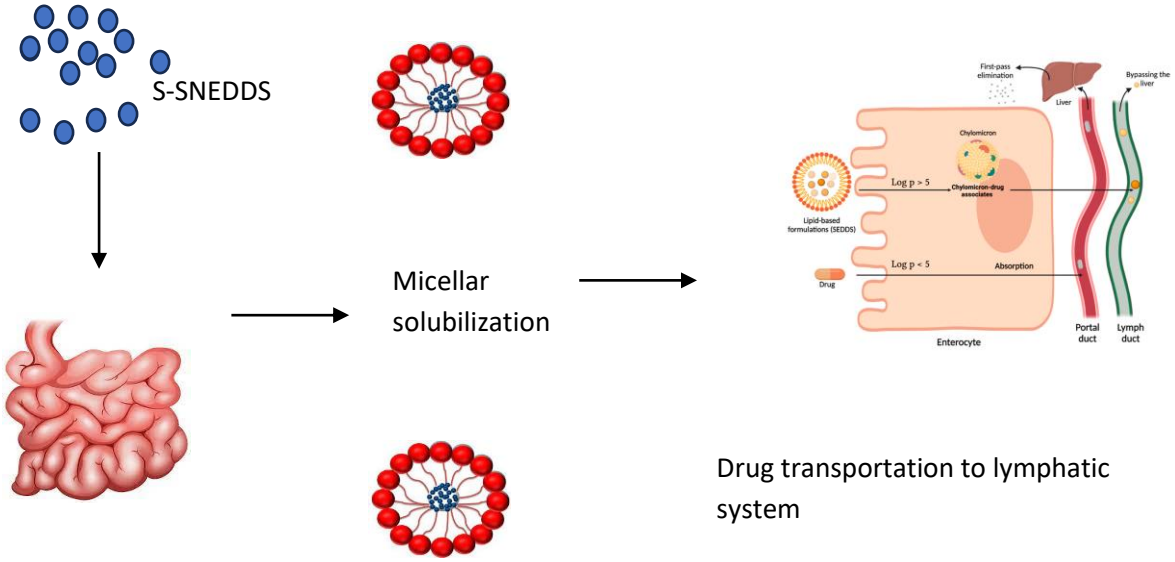
Disadvantages of SNEDDS [11]

- The *in-vitro* models of SNEDDS require additional research and validation for strength evaluation.
- The *in-vitro*-in vivo correlations of SNEDDS require further investigation.
- Conventional dissolve techniques cannot be employed for SNEDDS since they rely on digestion before dissolution.
- The chemical instability of pharmaceuticals; greater usage of surfactants (30–60%) in formulation; increased production costs; decreased medication stability and incompatibility; and potential for drug leakage and precipitation.

SNEDDS Mechanism of Action

Solid SNEDDS in the form of tab/cap undergo disintegration the dissolve completely in the gastric fluid upon gentle agitation**.** [12] When the SNEDDS is administered, it causes a mild agitation due to gastrointestinal motions, which causes an oil-in-water nano-emulsion to form instantly and spontaneously with particles in the nanometric range (less than 200 nm). A better interfacial surface is provided by these drug-containing nanoparticles, which were previously dissolved in the oil phase, to aid in the drug's dispersion into GI fluids. [13] By changing the transport property, this increased interfacial area improves medication

permeability and solubility. [14] Drug absorption into the gastrointestinal tract occurs more quickly in nanosized droplets due to their rapid digestion.



General Components of SNEDDSs

Pouton introduced the lipid formulation classification system (LFCS). SNEDDSs are classified as class III compositions by LFCS. These compositions consist of oils and water-soluble surface-active agents, such as cosurfactants and surfactants, with the possibility of cosolvents as well. When choosing formulation ingredients, care must be taken to create a successful SNEDDS. [5]

A. Lipophilic components (oils)

SNEDDSs are typically made of Medium- and Long-Chain Triglycerides (TG) containing oils with different saturation levels. Since oil plays a major role in both drug absorption and formulation loading capacity, the oil with the greatest capacity to solubilize a particular medication is typically chosen. Although natural edible oils, such as castor, soybean, and coconut oils, are still the most desirable and logical oil components, their emulsification efficiency is low and their drug-loading capacity is relatively low. The primary purpose of modified medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) in formulations is to improve medication solubility and the lipophilic phase described in the table.

List of oils used in the formulation of SNEDDS [68,69,70]

Category	Excipients name	HLB value
	Capmul® MCM	5.5
Medium Chain Triglycerides	Captex® 355	1
	Labrafac® CM 10	10
	Imwitor® 742	3-4
	Peceol®	3.3
Long Chain Triglycerides	Cithrol® GMS 40	3-5
	Plurol oleique® CC 497	6

Triglycerides with lipid chains that vary in length from C8 to C10 make up the majority of MCTs (i.e capryol® 90, captex® 300) In contrast, TG (Triglycerides) in LCTs (Long Chain Triglycerides) have lipid chain lengths longer than C10 (i.e Lauroglycol® 90, peceol®) [15,16,17] MCTs are favored due to their superior potential for self-emulsification and solubilization. [18] The only enhancer that has been therapeutically applied to the intestines for enteral medication distribution is still C10. [15] MCTs have a limited ability to improve drug transport via the lymphatic system [LCTs avoid the FPM], but they can increase drug transport via the portal vein. [19,20] Therefore, to achieve ideal qualities and enhance pharmacokinetics profiles, a combination of MCTs and LCTs may be taken into consideration.

Bile and pancreatic fluids are secreted because of lipid components, which also create mixed micelles that contain cholesterol, phospholipids, and bile salts. The creation of such micelles significantly increases the solubility of components that are poorly soluble. [19,20]

B. Surfactants

Surfactants (30-60% are generally used) can dissolve large amounts of hydrophobic medicines in the gastrointestinal lumen without precipitating them because of their amphiphilic nature. Because of their superior safety profiles, natural surfactants are chosen over synthetic ones. Although lecithin, a natural surfactant with high biocompatibility, is the most suited, its efficiency in self-emulsification is limited. [21] They create a more stable nano-emulsion by concentrating at the oil-water interface and settling at the inner stage (internal phase) of the emulsion. [22,23]

The most promising emulsifiers are non-ionic surfactants, particularly those with high HLB values (HLB >12) and low toxicity (Gelucire® 50/13, Gelucire® 44/14, Cremophor® EL, Cremophor® RH 40, Labrasol®). Additionally stabilizing emulsions created throughout a wide range of pH and ionic strength are non-ionic surfactants.[24] When creating the formulation for SNEDDS, safety concerns about the cytotoxicity and permeability of surfactants must be considered, as their high concentration may irritate the gastrointestinal tract. [25,26] Surfactants are classified as non-ionic and ionic (anionic, cationic, and zwitterionic) based on the charge they carry. Non-ionic surfactants are typically utilized instead of ionic surfactants due to their reduced toxicity and capacity to stabilize emulsion over a larger range of nano-emulsion pH and ionic strength. [27] After enteral administration, some of them may irritate the GI epithelium. As a result, SNEDDS need to keep their surfactant content as low as feasible.

List of surfactants used in the formulation of SNEDDS [68,69,70]

Category	**Excipients name**	**HLB value**
	Acconon® C- 44	13
	GELucrine® 44/14	14
	Kolliphor® HS 15	14
PEG esters	Cremaphore® RH 40	14
	Labrasol®	14
	Tween® 20	16
	Tween® 80	15

C. Cosurfactants

They can work in concert with surfactants to improve the drug's solubility and the surfactant's dispersibility in the oil, which will increase the stability and homogeneity of the nano-emulsion. [28] By increasing interfacial fluidity, the use of cosurfactants or cosolvents might lessen the surfactant's local irritancy and the formulation's dosage variability. [29] Therefore, cosurfactants are used to lower the surfactant concentration, dissolve a significant amount of hydrophilic or lipophilic medication in the lipid base, and reduce the oil/water interface, which causes an instantaneous microemulsion to occur. Cosurfactants with hydrophile-lipophile balance (HLB) values between 10 and 14 are frequently used with surfactants to significantly lower interfacial tension, achieve a temporary negative value, and provide the

interfacial layer enough flexibility. [30-35] Propylene glycol, ethanol, poly (ethylene glycol) (PEG), and other more recent cosolvents like Transcutol® HP are often used cosolvents. [36,37] After aqueous dispersion, the cosolvent migrates easily into the water phase, causing drug precipitation. [38] Moreover, medication precipitation may occur from alcohols and other volatile cosolvents evaporating into the capsule shell. [39] In addition to the components already mentioned, extra substances such as antioxidants, viscosity enhancers, and compounds for modified drug release can be added to the SNEDDS formulation. [40-43]

List of Cosurfactnats used in the formulation of SNEDDS [68,69]

Excipient class	**Examples**
	Transcutol® HP
Diethylene glycol monoethyl ether	Transcutol® P
	Ethanol
Organic solvents	Propylene Glycol
	Poly Ethylene Glycol

Solid carriers

Probable effects of solid carrier characteristics on how they interact with lipids in medication formulation and solubilization. [44] To compress tablets, the optimal solid carrier should have a high capacity for lipid loading, dispersibility, acceptable flow properties, and sufficient mechanical strength. [45] These carriers may be soluble in water or insoluble in water. Polymer, protein, and polysaccharide-based carriers are examples of water-soluble solid carriers. The group of water-insoluble carriers includes certain aluminosilicates and carbonates, as well as porous and non-porous silica adsorbents. Novel solid carriers with properties appropriate for creating lipid-based drug delivery systems include mesoporous carbon, porous carbonate salts, polysaccharides, and clay-based materials. [46] There have been reports of increased drug release in conjunction with increased silica pore size and hydrophilicity in formulated formulations. There was no reduction in drug release during storage since the used silicas were macroporous and lacked mesopores. [47] Due to an increase in water penetration into the pores, PVP coating over silicas demonstrated full drug release. [48]

Because liquids adsorb into the pores in Neusilin® US2, this carrier was the only one that produced tablets with the necessary tensile strength when the lipid component was present in an equal ratio. [49] The most widely used adsorbent is silicon dioxide, however, it is not

biodegradable. Exposure to silica nanoparticles, even at the microscale level, has been linked to the development of several autoimmune diseases, including lung cancer, rheumatoid arthritis, systemic sclerosis, renal failure, lupus, and silicosis. Strengthen medicinal effectiveness and bioavailability by employing coffee husk acidification as an inexpensive, biodegradable biosorbent. Coffee husk powder is a low-cost alternative to the expensive synthetic Adsorbent, it is non-toxic, easily available ad effective adsorbent.[50]

Singh. H *et al* using three different solid carriers in the formulation of DHA-loaded S-SNEDDS and the carriers are Carbohydrates (lactose, mannitol), Complexing agents (extrin, maltodextrin, β-cyclodextrin), polymers (Hydroxy Propyl Methyl Cellulose (HPMC), soluble starch). Spray drying method was employed in formulation of S-SNEDDS. Above mentioned carriers are hydrophilic and the liquid SNEDDS were adsorbed on to the carrier.[71] Beg. S *et al* developed Valsartan-loaded S-SNEDDS using a porous carrier like aerosil 200 (conversion of liquid SNEDDS into free-flowing solid granules), solidification of liquid achieved by the simple adsorption method (easiest and efficient method), this is further developed to tablets o filled into capsules. [72] Schmied F. P *et al* prepared celecoxib, efavirenz and fenofibrate loaded stable Solid Self Nano Emulsifying Drug Delivery System (S-SNEDDS) using copolymers such as polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol, polyvinylpyrrolidone-polyvinyl acetate copolymer, Polyvinylpyrrolidone, Hydroxy propyl Methyl Cellulose, Dimethylaminopropyl- methacrylamide-butyl methacrylate-methyl methacrylate copolymer, modified Eudragit® by Hot Melt Extrusion (HME) method.[73]

List of solid carriers used in the formulation of SNEDDS [71]

Solid carriers	**Properties**
Neusilin US 2	High absorption of oils, surface area is high, Decreased particle size, highly porous and uniformly size.
Cellulose derivatives (Hydroxy Propyl Cellulose, Hydroxy Propyl Methyl Cellulose)	Viscous in nature, used as precipitant inhibitors.
Starch, lactose monohydrate, maltodextrins	Solubilize the aqueous phase.
Coffee husk powder	Naturally obtained carrier, non-toxic, highly porous structure.

Selection of drug candidate for SNEDDS

One of the issues a formulator faces when creating an enteral dosage form is getting the medication to dissolve in the gastrointestinal tract. The pace and extent of medication absorption are enhanced by SNEDDS. The SNEDDS method is used for BCS class II medications that have poorer bioavailability and water solubility. [51] When these medications are administered as lipids, they become more bioavailable because they get beyond the lower water solubility absorptive barrier and move to the bile-salt mixed micellar phase in the gastrointestinal tract, where absorption is easier. [5] Medication characteristics, such as water solubility and log P, are insufficient to determine if a lipid-based formulation is appropriate because they cannot foretell the effects of the medication *In-vivo*. [52] The free energy needed to make an emulsion in SNEDDS formulation might be either small, positive, or negative. Emulsification thus occurs spontaneously. For emulsification to occur, the interfacial structure must demonstrate that there is no confrontation against surface shearing. The simplicity of water penetration into a range of liquid crystalline or gel phases on the droplet surface could be the cause of the ease of emulsification. [53]

Recent advancements in SNEDDS formulation

Supersaturated SNEDDS

In normal SNEDDS formulations, the oil content may be reduced due to digestion, this will lead to precipitation of drug because of decreasing the solubility of drug.[79] To overcome the problem addition of Polymeric Precipitation Inhibitors to the formulation, this is known as a supersaturated SNEDDS (s-SNEDDS). [80] In this case polymers are employed as a precipitation inhibitor such as polyvinylpyrrolidone (PVP), Hydroxy Propyl Methyl Cellulose (HPMC). This formulation has increased solubility, stability GI absorption, reduce toxicity and improved safety. [81]

Solid SNEDDS

Liquid formulation of SNEDDS have some disadvantages like interaction with the capsule shell, poor handling, stability problems, storage of formulation. These problems are overcome by conversion of liquid formulation into solid form (Solid SNEDDS). [46] This solidification process is done by various methods like Adsorption into inert carriers, [72] spray drying, [82] melt granulation, [83] melt-spherization method. [84]

Mucous permeating SNEDDS

Mucous is the barrier for the drug permeation, mucous rapidly secreted and blocks the drug to reach the GI epithelial cells. [85] SNEDDS with smaller globule size and SEDDS with PEG lated surfactants increase the permeability through the mucous, SNEDDS are highly mucous inert nature. [86] Friedl *et al* demonstrated 70% of drug permeate mucous when it has globule size of 12nm whereas larger globule SNEDDS permeate very low in amount (only 8%).[87] Mucolytic agents also increase the drug permeation to the GI epithelium, mucolytic agent breakdown the mucous barriers. [88]

Recently developed enteral administration of SNEDDS

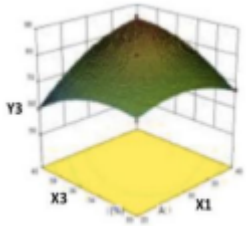
Drug name	Composition	Dosage form
Ritonavir	oleic acid, Cremaphor® RH 40, ethanol	Soft gelatin capsule
Sirolimus	Phosphatidyl choline, soy fatty acids, mono and di glycerides, ethanol, propylene glycol, Ascorbyl palmitate.	Enteralsolution
Cyclosporine	Corn oil or olive oil, Labrafil® M 1994 CS, ethanol, α-tocopherol	Soft gelatin capsule
Isotretinoin	Beeswax, hydrogenated soyabean oil flakes, hydrogenated vegetable oil, soyabean oil, olive oil, polyoxyethoxylated oleic glycerides, ethanol	Soft gelatin capsule
Tipranavir	Mono and di glycerides of caprylic acids, Cremaphor® EL, ethanol, Propylene glycol	Soft gelatin capsule

Construction of Nano phase map (Pseudo ternary diagram)

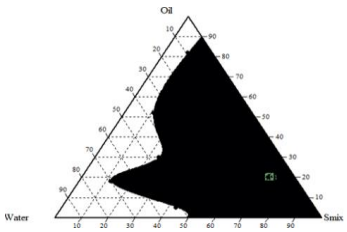
Pseudo-ternary phase charts for different sets of Using the aqueous phase titration approach, pseudo-ternary phase diagrams for several combinations of surfactants and cosurfactants were created, as previously reported. [54,55] A mass ratio of 1:1 was used to premix each surfactant and co-surfactant. To accurately define the phase boundaries created in the phase diagrams, oil phase and a particular S mix were thoroughly mixed in varying mass ratios (1:9 to 9:1). After gradually adding aqueous phase to the mixture of oil phase and particular S mix, visual observations were taken following each addition of water to titrate the mixture. [55] Systems that were easily flowable and transparent were classified as SNEDDS. A pseudo-ternary phase diagram was used to indicate each formulation's physical state.

Box-Behnken design is a response surface design that offers a suitable model for the quadratic behavior of factors. It is based on three levels (−1, 0, +1). [56] The formula N = 2k (k

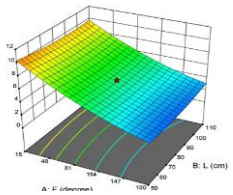
− 1) + C0 gives the number of runs (N) required to construct the Box–Behnken design, where k and C0 are the numbers of independent variables and central points, respectively. SNEDDSs of polypeptide-k were developed by Garg et al. [57] and optimized using Box-Behnken design (Figure a). To investigate the effect of SNEDDS factors on the chosen answers (dependent variables), seventeen runs were conducted. According to the study, size grew at increasing levels of cosolvent (diethylene glycol monoethyl ether, X3) and oil (oleoyl polyoxyl-6 glycerides, X1), but size decreased at higher levels of surfactant (Tween® 80, X2). Along with the increases in the X1, X2, and X3 ratios, the drug loading (Y3) also increases.



A. Box Behnken Design



B. Pseudo ternary phase diagram



C. Central Composite Design

Bosentan-loaded SNEDDSs made of PEG 600 (cosolvent, X3), MCM (oil, X2), and Capmul® and Labrasol® (surfactants, X1) were optimized by Panigrahi et al. [58] using a central composite design. Surfactant and oil were identified as significant components in SNEDDSs by preliminary Taguchi design investigations, which were then further screened and optimized using a central composite design. The independent factors are Particle size (Y1), Emulsification time (Y2) and % drug release (Y3). A low level of oil and a high level of surfactants decrease the particle size, decrease emulsification time and increase the drug release.

Sultan Alshehri *et al.* [59] developed Full Factorial Design, Lipid (X1), surfactant (X2), and droplet size (Y1, nm), zeta potential (Y2, mV), and polydispersity index (PDI, Y3) were used as independent variables in the FFD. Additionally, the pure FLF suspension and the improved formulation (OFS1) were compared and described.

Characterization of S-SNEDDS

Determination of self-emulsification time [66]

When in contact with water and gently agitated, an ideal SNEDDS formulation can naturally create an emulsion. USP type II (paddle) was used to evaluate the self-emulsification efficiency at 100 rpm. The emulsification media, 0.1 N HCl, was kept at 37±0.50C. The paddle was revolved at 100 rpm after 1 ml of L-SNEDDS was dropped dropwise into 100 cc of the medium. For every formulation, the self-emulsification time was recorded.

Determination of % Transmittance [79]

Distilled water was used to dilute the L-SNEDDS formulations 100 times. With a UV-visible spectrophotometer, the produced emulsion's transmittance was tested at 650 nm. As a blank, distilled water was utilized.

Determination of Viscosity [66,79]

The viscosity of the microemulsion formulations that were created was measured using a Brookfield DV III ultra V6.0 RV cone and plate rheometer without any dilution.

a. After dilution with water

It was found that the diluted SNEDDS had a viscosity. It was found that the diluted SNEDDS had a viscosity. Diluted SNEDDS's viscosity reveals the kind of emulsion that was created. When an emulsion forms, low viscosity suggests w/o emulsion, while high viscosity indicates o/w emulsion. The type of produced emulsion is displayed by SNEDDS. High viscosity denotes the presence of an o/w emulsion, while low viscosity suggests the formation of a w/o emulsion.

Assessment of mean droplet size

Since mean droplet size analysis has a significant impact on drug release, the lipolysis process, and ultimately drug absorption, it is useful for estimating the efficiency of S-SNEDDS formulations. For figuring out the mean droplet size of diluted SNEDDS, photon correlation spectroscopy, [61] laser diffraction, and Coulter counting [60] are often employed techniques. It is highly recommended to combine these indirect methods, which rely on specific assumptions, with a direct measuring method such as microscopy.

One of the most important tests for developing SNEDDSs is size characterization since the size of the particles can directly impact both the *In-vivo* efficacy of an SNEDDS (drug absorption) [75,76] and the *in-vitro* assessed features (dissolution, stability). Research has shown that a medicine encapsulated in SNEDDSs has improved enteral bioavailability when the particle size is lower. [77,78]

Determination of PH:[66]

A pH meter was used to determine the SNEDDS pH values.

Zeta Potential: [67]

The dispersion medium's zeta potential determines the surface charge of the produced droplets and indicates their stability. The droplets' electrophoretic mobility is measured to ascertain it. The charge on a droplet has a crucial role in enhancing drug absorption, even though zeta potential is not more relevant for determining the stability of the emulsion in the case of SNEDDS. This is because the negatively charged membrane and positively charged droplets interact effectively.

In-vitro drug release Performance: [66,74]

The dialysis bag approach was used to carry out the investigation. Specification for dialysis membranes. The cellulose membrane was the dialysis membrane employed in the investigation (Sigma, USA). Untreated tubing is kept at room temperature for storage. With an average flat width of 2.5 mm and a diameter of 16 mm, it had a capacity of 60 mL/foot.

Stability studies:

The stability investigation was conducted for three months at 40 C and 75% ± 5% RH to ascertain the temperature sensitivity on the dissolution release profile, emulsion droplet size, PDI, and drug content of optimized S-SNEDDS. Drug content, PDI, emulsion droplet size, and dissolution release profile were assessed for the stability samples. The drug content, emulsion droplet size, PDI, and *in-vitro* drug release tests did not significantly alter in samples that were removed after three months, there was no discernible variation in the drug content, emulsion droplet size, and PDI data.

CONCLUSION:

Various novel drug delivery systems are available in the pharmaceutical field but S-SNEDDS is the promising approach for increasing the solubility and bioavailability of poorly water-soluble drugs (BCS class- II drugs). This could enhance the solubility by using various surfactants (non-ionic) and cosurfactants. Solid SNEDDS have the advantages of reducing drug degradation, improving handling, increased dose accuracy. S-SNEDDS are prepared by various methods, adsorption onto the carrier is the simplest method. S-SNEDDS sustain the drug release when incorporated with rate control polymer. Many anti-cancer, anti-hypertension, anti-hyperlipidaemic, anti-viral solubility, stability, bioavailability are increased by formulating via S-SNEDDS. Due to the ease of manufacturing, drug targeting, improved drug performance (efficiency), desired pharmacokinetics and decreased adverse reaction, future research shall be based on S-SNEDDS. Modification on the S-SNEDDS should make more attractive the formulation.

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