A Comprehensive Review on Self-Nanoemulsifying Drug Delivery Systems (SNEDDS): Recent advances

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Abstract

The literature extensively discusses the lipid-based drug delivery strategy for improving drug solubility, permeability and bioavailability. The great majority of new pharmacologically active substances developed in current drug discovery programmes are lipophilic and poorly soluble, which creates a substantial challenge for pharmaceutical researchers tries to increase the oral bioavailability of such therapeutic molecules. Drugs with poor dissolution rate and insufficient absorption can be administered using self-nanoemulsifying drug delivery system (SNEDDS), which is effective oil-based method. Ever since the progress of SNEDDS, researchers have been concentrating on the difficulties of BCS Class II and Class IV pharmaceuticals for increasing water Solubility of poorly water-soluble pharmaceuticals. For improving the solubility and bioavailability of lipophilic drugs, SNEDDS is a promising technique. It helps to reduce interfacial tension and increase the rate at which drug molecules dissolve and absorbed. It consists of an isotropic blend of oil, surfactant, co-surfactant and/or co-solvent molecule. which when diluted with water while being gently stirred, generate an oil-in-water nano emulsion with a size of about 200 nm or less. It's drug delivery method has both kinetic and thermodynamic stability. The physicochemical characteristics and drug solubilization potential significantly influence the choice of SNEDDS components. Phase diagrams are frequently used to aid in the optimisation of the SNEDDS compositions. With the use of statistical experimental design, SNEDDS may be further optimised. It is a novel drug delivery technology that may be used for cosmetic, parenteral, ophthalmic and intranasal drug administration. The preparation, components, mechanism of self-Nano emulsification, characterization techniques and applications of the Self-nanoemulsifying Drug Delivery System (SNEDDS) are all covered in the present review.

Introduction

LBDDS, or lipid-based drug delivery systems, are the most promising method for manufacturing pharmaceuticals that are poor water soluble. Over the past few decades, various lipid-based formulations have been investigated to enhance the oral delivery of lipophilic drugs which include liposomes, solid lipid nanoparticles (SLNs), lipidpolymer hybrid nanoparticles, microemulsions, nanoemulsions, lipid containing micells, nanostructured lipid carriers (NLC), self-micro emulsifying and nanoemulsifying drug delivery systems (SMEDDS and SNEDDS). But the most widely used lipid-based strategy in recent years to improve the aqueous solubility of BCS Class II and IV Drugs that are naturally poorly water-soluble is self-emulsifying drug delivery systems (SEDDS), particularly the Self-Nano emulsifying Drug Delivery System (SNEDDS). The use of SNEDDS is a critical strategy which combines the advantages of LBDDS with nanotechnology so, SNEDDS are currently favoured to enhance the formulation of drugs with low water solubility.[1] Nanotechnology now plays a crucial role in drug delivery studies and has a significant impact on the therapeutic effectiveness of hydrophobic (lipophilic) drugs.[2] The stability of nanoemulsions and their ability of simple oral administration to enhance drug self-emulsification in the gut make them the ideal drug delivery system. The self-nanoemulsifying Drug Delivery system has been developed using medium chain tri-glycerides oils and non-ionic surfactant, which was vital for oral administration.[3] Self-nanoemulsifying drug delivery systems (SNEDDS) are isotropic compositions of an active pharmaceutical ingredient in a mixture of natural or synthetic lipids/oils, surfactants, and water-soluble co-solvents or co-surfactant.[4] These combinations of anhydrous liquids are frequently referred to as pre-concentrates.[5] These pre-concentrates when gently stirred by the digestive system in an aqueous phase such as the upper GI lumen content, form drug-encapsulated ultrafine oil in water(o/w) self-nanoemulsion or *in situ nano*emulsion with a particle diameter of 200 nm or less.[6][7] This spontaneous emulsion formation in the gastrointestinal system solubilizes the drug. The SNEDDS are also crucial for producing a large interfacial area for hydrophobic drug partitioning between the oil and aqueous phases, enhancing the drug's total bioavailability.[8]

Properties of SNEDDS:[9]

1. They have the ability to quickly self-emulsify in digestive fluids and form a fine o/w emulsion under the influence of the mild agitation generated by peristaltic and other movements of the gastro intestinal tract.

2. Both hydrophobic and hydrophilic drugs can be successfully incorporated into the oil surfactant mixture.
3. Compared to conventional dosage forms, they require a smaller amount of the drugs.
4. They can be used for both liquid and solid dosage forms.

Selection of aprropriate drug for SNEDDS formulatin

The SNEDDS system is a novel approach to improve oral bioavailability of poorly water-soluble drugs. Class II and Class IV medications have lower water solubility than Class I and Class III pharmaceuticals in the Biopharmaceutical classification system (BCS), which may be divided into four categories.

A schematic representation of the Biopharmaceutical Classification System (BCS), which has four classes of system and is illustrated in Figure 1, is based on the solubility and permeability study.[10]

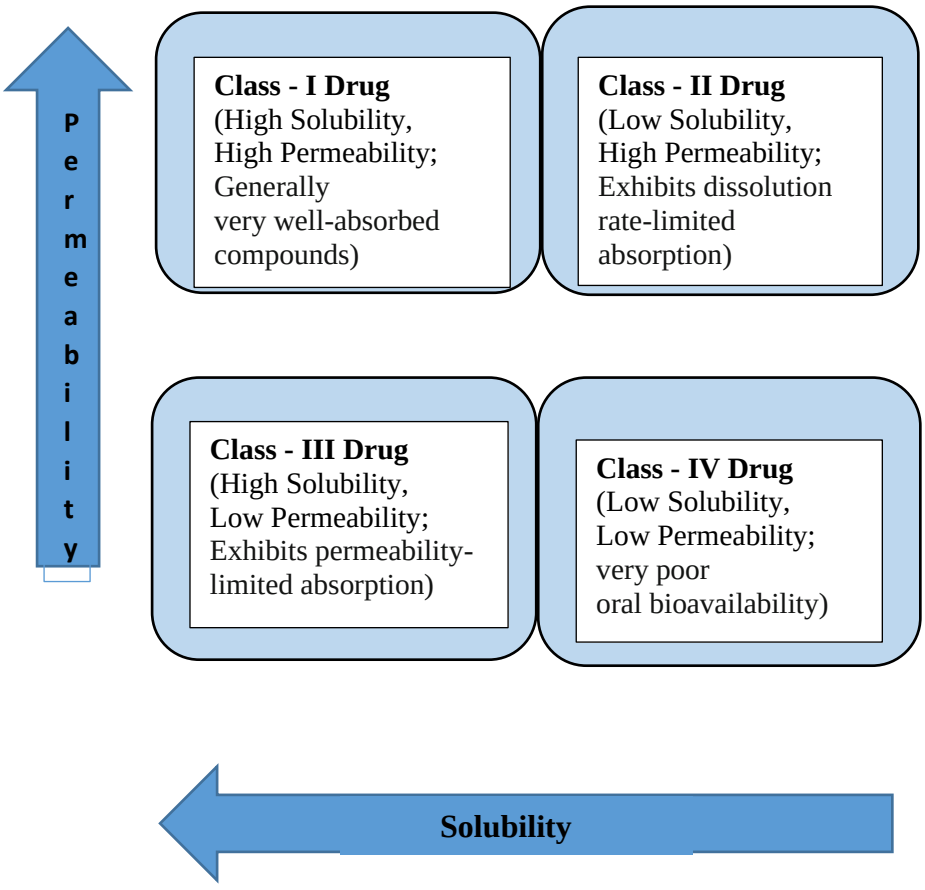


Figure 1. BCS classification of drugs

Class II and Class IV medications can improve their oral bioavailability and water solubility under the Self-Nanoemulsifying Drug Delivery System. The SNEDDS is important to prevent enzymatic degradation problem associated with Class I Drugs and Class III Drugs and Improved Solubility and Bioavailability.[11]

By avoiding the barrier of lower water insoluble solubility, lipidized versions of Class II and Class IV medications improve their absorption. They also demonstrate how their dissolution in the gastrointestinal tract by membrane transfer to the bile-salt mixed micellar phase. This allows for easy absorption.[12] In this aspect, the drug's characteristics, such as its water solubility and log P, do not adequately illuminated whether a lipid-based formulation would be beneficial since they are unable to predict the effects in vivo.[13]

Table 1. Advantages and disadvantages of SNEDDS

Advantages	Disadvantages
High drug entrapment efficiency	Risk of drug leakage and precipitation.
SNEDDS are thermodynamically and kinetically stable[5]	High production cost.
SNEDDS are manufactured using simple methods and a very stable composition.	Lower drug incompatibility and safety.
Drug diffusion using SNEDDS made it possible for a broader distribution throughout the GI tract and stomach, which decreased irritation triggered on by increased contact between the drugs and the gut walls.	Conventional dissolve techniques are unsuccessful for SNEDDS because of their dependence on digestion before disintegration.[14]
SNEDDS shields the drug from the harmful conditions in the GI tract.	Chemical instability of drugs.
SNEDDS manage controlled drug delivery profile.	The formulation's surfactant concentrations are more (30–60%).[15]
In terms of surface interfacial area, SNEDDS assist for improved drug partitioning between water and oil.	More study and validation are needed for SNEDDS in vitro models in order to evaluate strength.[14]
SNEDDS dissolves large amount of lipophilic drugs.	

SNEDDS enhance the drug's pharmacokinetics, which lowers the dosage frequency.[16]	
With the help of SNEDDS, drugs may be specifically targeted to the GI tract's specific absorption window.	
The rate and extent of medication absorption are increased by SNEDDS.[17]	

Composition of SNEDDS:

The following are the primary elements of the SNEDDS:

- Drug
- Oils/Lipids
- Surfactant
- Co-surfactant/ Co-solvent

Drug:

Drugs with a poor water solubility are frequently accommodated by SNEDDs. The majority of the time, BCS class II and class IV medications are utilised in the production of SNEDDs. The performance of SNEDDS is significantly influenced by the physicochemical characteristics of the medication, including log P, pKa, molecular weight, presence of ionizable groups, and quantity.[18]

Drugs with high melting points and log P values of less than 2 are not well suited for SNEDDS. whereas, lipophilic medications with log P values more than 5 are a promising choice for SNEDDS.[19]

Table 2. Some examples of drug formulation formulated as self-nanoemulsifying systems

Drug	**Dosage form**	**Benefits**	**Reference**
Rutin	SNEDDS	Enhance oral bioavailability and efficacy	[20]
Talinolol	SNEDDS	High drug-loading capacity, improved drug dissolution, increased gut permeation, reduced/no toxicity and enhanced oral bioavailability	[4]
Ritonavir	SNEDDS	Improve oral bioavailability	[21]
Paclitaxel	SNEDDS	Improvement in the oral bioavailability	[22]
Nifedipine	SNEDDS	Increase bioavailability	[23]
Itraconazole	SNEDDS	Improve topical antifungal Property	[24]
Irbesartan	SNEDDS	Enhance oral bioavailability	[25]
Glibenclamide	SNEDDS	Enhancement of solubility and dissolution	[26]
Furosemide	SNEDDS	Enhance dissolution rate of Furosemide	[6]
Docetaxel	SNEDDS	Improve oral bioavailability and its chemotherapeutic effect. Exhibited a remarkable antitumor efficacy with a reduced toxicity.	[27]
Cinnarizine	SNEDDS	Great potential to enhance the oral delivery	[28]
Carbamazepine	SNEDDS	Faster absorption into the systemic circulation.	[29]

		Erratic absorption and presystemic efflux is predominantly reduced.	
Amphotericin B	SNEDDS	Improve the oral bioavailability.	[30]

Oils:

The choice of a particular oily phase is a crucial consideration when choosing the components for a nanoemulsion in a self-nanoemulsifying drug delivery system (SNEDDS), and it is mostly connected to O/W nanoemulsion. When choosing an oily phase for a nanoemulsion formulation, the oil is crucial for the drug candidate's maximal solubilizing capacity. This strategy is crucial since it has a large capacity for drugs loading.[31]

For easier self-emulsification, to increase the amount of medicine moving through the intestinal lymphatic system, and to solubilize the lipophilic drug, the oil is utilised in the SNEDDS formulation. This improves absorption. With various saturations, long- and medium-chain triglycerides (LCT and MCT) are used. Triglycerides are highly lipophilic oily molecules, and the solvent capacity of drugs is frequently a function of effective concentration in ester groups. Triglycerides with long chain fatty acids consist of the combination of oils and fats that occurs naturally as well as synthetically. The classification of triglycerides as short chain (5 carbons), medium chain (6–12 carbons), or long chain (>12 carbons) is crucial for lowering the level of unsaturation and preventing oxidative degradation. Compared to long chain triglycerides, medium chain triglycerides (MCT) molecules have a higher solvent capacity and greater ability to resist oxidation. To improve the water solubility of medications that are poorly soluble in water, new semi-synthetic medium-chain molecules called as amphiphilic compounds which have surfactant properties have taken the position of MCT.[32] Vegetable oils, digestible or non-digestible oils, and fats, such as sesame oil, soybean oil, oleic acid, maize oil, palm oil, and corn oil, are used to modify oil phases to increase their solubility.

The difficulty of edible oils to solubilize higher drug concentrations is the reason they were not chosen for the SNEDDS formulation. Due to the creation of improved emulsification systems with more surfactants approved for oral administration, hydrolyzed vegetable oils are employed. They promoted formulation and physiological compensation.

Table 3. Examples of oils used in SNEDDS:

Lipids and oils	Fatty acids	Palmitic acid, Stearic acid, Oleic acid
	Fatty acid and esters	Glyceryl monooleate, Glyceryl monostearate, Glyceryl monolinoleate, Glyceryl palmito stearate, Glyceryl behenate, Ascorbyl palmitate, Medium chain mono- and diglycerides, Medium chain triglycerides, Glyceryl dilaurate, Propylene glycol monolaurate.
	Propylene Glycol esters	Propylene Glycol monocaprylate, Propylene glycol dicaprylocaprate
	Miscellaneous	Stearyl alcohol, Phospholipids, Beeswax, Vitamin E

Surfactant:

Selection of a suitable surfactant is essential for the preparation of SNEDDS. The surfactant's characteristics, including its HLB, cloud point, viscosity, and affinity for the oily phase, have a significant impact on the nanoemulsification process, the self-nanoemulsification area, and the size of the nanoemulsion's droplets. The amount of surfactant present in SNEDDS has a significant impact on the size of the droplets in nanoemulsions.[33] The size of the droplet ultimately increases along with the surfactant concentration.[34] During the surfactant selection process, it is also important to take into account the chosen surfactant's regulatory status, such as its generally regarded as safe (GRAS) status, as well as its suitability for the intended route of administration. It should be highlighted that surfactants are not harmful and that their biological effects depends on the chemical nature of the substance as well as their concentration. Several nonionic surfactants, such Cremophor EL (polyethylene glycol [PEG]-35-castor oil), have the power to increase the permeability and absorption of medications that are sensitive to P-glycoprotein-mediated efflux.[35] However, these surfactants may also have negative effects that depend on the structure, concentration, and route of delivery; for example, Cremophor EL can result in anaphylactic shock and histamine release with parenteral treatment[36], However, when given orally, it is well tolerated.[19] Higher doses of certain

surfactants may irritate the GI mucosa and skin. Furthermore, it should be noted that the unfavourable properties of the surfactant may change after connection with the oily phase. For example, the hemolytic ability of surfactants in submicronic emulsions was significantly diminished after association with the oily phase.[37] Cuine and colleagues have shown that the surfactant structure and concentration can affect the drug precipitation in the GI tract, which in turn affects the drug's bioavailability.[38] Therefore, the choice of surfactant is key for the development of SNEDDS and the concentration of surfactant in SNEDDS should be kept as low as possible. It is possible to develop SNEDDS using a variety of surfactants, either alone or in combination, to produce nanoemulsions with desired properties while avoiding or minimising the unfavourable impacts of that surfactant.[39]

In comparison to ionic surfactants, nonionic surfactants are more stable, nontoxic, having high hydrophilic and lipophilic balance (HLB) and are thermodynamically stable. It is an essential component in the formulation of a nanoemulsion system that will increase the solubility of drugs having low water solubility.[40]

Classification of Surfactant:

Surfactants are mainly classified into four types:

1. **Anionic surfactant**: An Anionic surfactant is a hydrophilic group that carries a net negative charge. The negatively charged groups include sulphonate (RSO3-), sulphate(ROSO3-) and carboxyl (RCOO-).

   Examples: sodium lauryl sulphate(SLS) and potassium laurate.
2. **cationic surfactants**: Cationic surfactants are hydrophilic groups that have a positive charge.

   Example: quaternary ammonium halide.
3. **Ampholytic surfactants/Zwitter or Zwitterionic surfactants:** Both positive and negative charges are present in the surfactant unit.

   Example: Sulfobetaines
4. **Non-ionic surfactant:**

   The hydrophilic group has no charge, but it can have highly polar functional groups like hydroxyl or polyoxyethylene HO-(CH2CH2O)n-H, which give it the ability to dissolve in water.

   Examples: polysorbates (Tween 20) and sorbitan esters (Spans).

Table 4. Examples of surfactantS used in SNEDDS

Surfactants	Caprylocaproyl polyoxyl-8-glycerides, Polyoxyethylene sorbitan fatty acid esters [Tweens], Polyoxyethylene castor oil derivatives, Polyvinyl alcohol, Sorbitan esters [Spans], Tocopherol polyethylene glycol succinate (TPGS) Hydroxypropyl methylcellulose, Poloxamer, Phospholipids and PEGylated phospholipids, Macrogol fatty acid glycerides, Polyvinyl pyrrolidone, Bile acids (sodium deoxycholate), Cellulose derivatives, Polyglyceryl-3 dioleate.

Co-surfactants:

Co-surfactants are utilised to enhance the surfactant's ability to emulsify. The co-surfactants are single chain surfactant units that can stop the fluidity at the interface. Preventing interfacial tension at the oil-water interface is a key function of co-surfactant in self-nanoemulsifying drug delivery systems (SNEDDS).[41] They can be included in SNEDDS for a variety of reasons, such as:

- To enhance the drug loading to SNEDDS;
- To adjust the SNEDDS's self-nanoemulsification time;
- To modify the nanoemulsion's droplet size.

The self-nanoemulsification zone in the phase diagrams may extend as a result of the cosurfactants or coemulsifiers being incorporated into SNEDDS. Co-surfactants are screened by creating isotropic mixtures by combining several co-surfactants with a chosen surfactant and oily phase under warming conditions. Once equilibrium has been reached, measurements of % transmittance, droplet size, and polydispersity index must be recorded.[14] A monomolecular layer of surfactant molecules can be used to separate the co-surfactant molecules from the surfactant, oil, and water molecules. The monomolecular layer of surfactant molecules is also referred as Liquid crystal formation layer.

As a coemulsifier or cosurfactant in the SNEDDS, we have investigated the potential of Akoline MCM® (short-chain mono- and diglycerides).[41] Propylene glycol, PEG, and glycol ethers (diethylene glycol monoethyl ether or Transcutol P) are some examples of amphiphilic solubilizers that are frequently employed in the SNEDDS to reduce the time needed for self-nanoemulsification and increase drug loading.[33],[42] In some cases, researchers have also utilised short-chain alcohols like ethanol.[43] However, although the fact that these solubilizers

can increase drug loading into SNEDDS, they may occasionally reduce the droplet size of the nanoemulsion, as observed by Anton and Vandamme.[44]

Table 5. Examples of cosurfactants used in SNEDDS

Co-surfactants /co-solvents /co-stabilizers	Propylene glycol, Phospholipids, Polyethylene glycol, Ethanol, Diethylene glycol monoethyl ether

Factors affecting SNEDDS:[14]

1. Nature and dose of the drug: Very high doses of drugs are not appropriate for SNEDDS unless they have excellent solubility in at least one of the components of SNEDDS, mostly the lipophilic phase. The most difficult drugs to administer via SMEDDS are those with poor solubility in water and lipids, often with log p values of approximately 2. The solubility of the drugs in oil phase has a significant impact on capacity of SNEDDS to keep the drug in solubilized state.
2. Concentration of Surfactant or Co-surfactant: There may be a risk of precipitation if the surfactant or co-surfactant is playing a larger role in the solubilization of the drug, as the dilution of SNEDDS will reduce the solvent capacity of the surfactant or co-surfactant.
3. Polarity of the Lipophilic phase: One of the factor that controls the drug release from nanoemulsions is the polarity of the lipid phase. The HLB, the length of the fatty acid chain and its degree of unsaturation, as well as the molecular weight of the drugs, all influence the polarity of the droplet.

Mechanism of Self Emulsification:

According to Reiss' theory, an emulsion forms when the entropy changes that favours dispersion is greater than the energy required to increase the surface of dispersion. As a result, the free energy (ΔG) of a conventional emulsion is a (negative) direct function of the energy needed to create a new surface between the two phases (oil and water phase), and the emulsion was stabilised. The relationship between the free energy of a traditional emulsion and ΔG can be represented using the following equation,[45]

$$\Delta G = \sum Ni\pi r_i^2\sigma$$

Where,

G: Free energy associated with process

N: Total number of droplets

r: radius of the droplets

σ: Interfacial energy

The interfacial area of an emulsion tends to decrease over time as the two phases separate. An emulsifying agent then stabilises the emulsion, forming a monolayer of emulsion droplets that reduces interfacial energy and acts as a barrier to prevent coalescence.[46]

PREPARATION OF SNEDDS

The Self-Nanoemulsifying drug delivery system (SNEDDS) is Prepared by two ways:

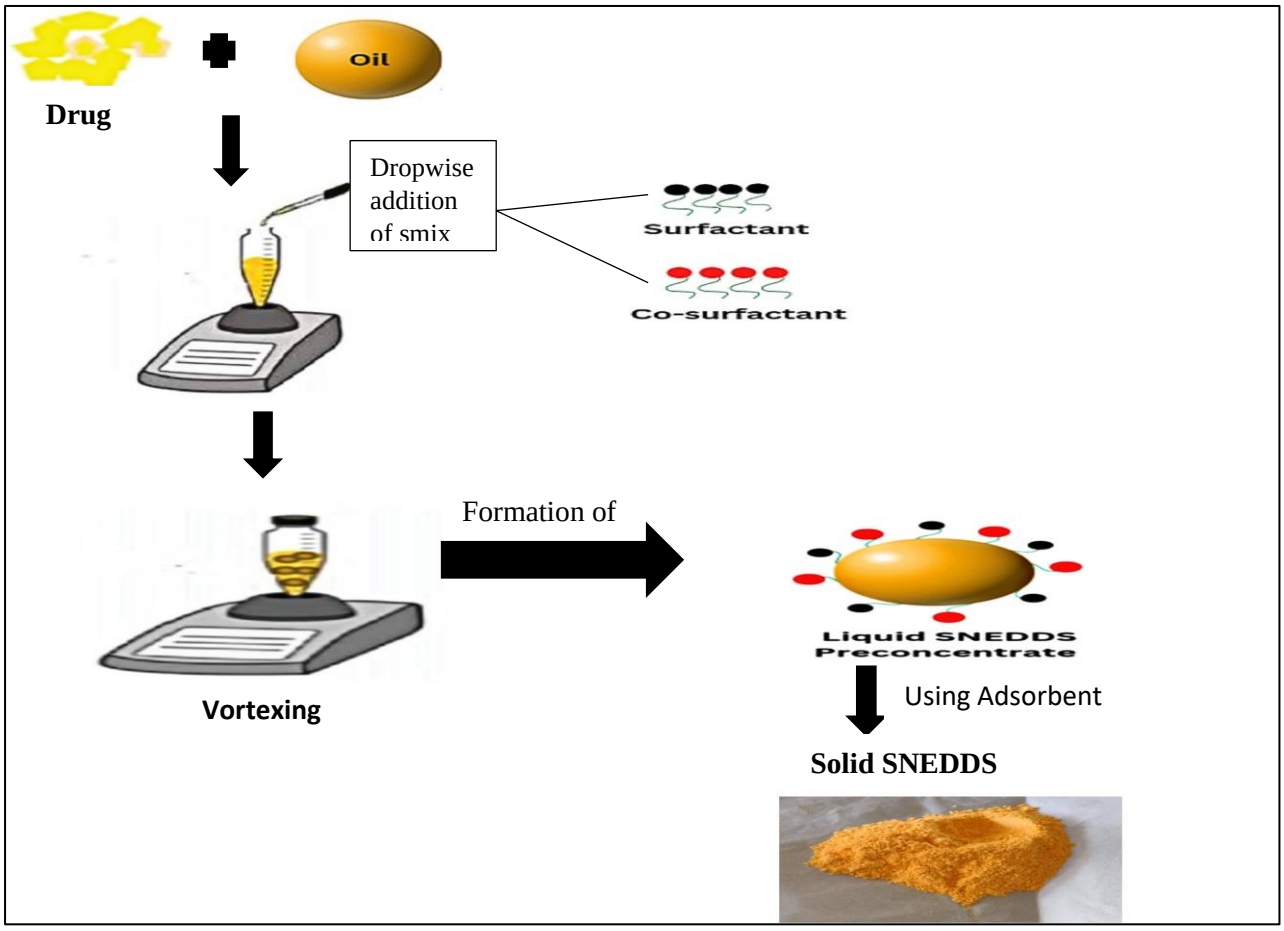
1. **Preparation of Liquid SNEDDS:**

   This is important technique to formulate a self-nanoemulsifying delivery system having the oil/surfactant/cosurfactant ratio and surfactant/co-surfactant ratio, which was selected from the pseudoternary phase diagram. Different oil, surfactant, and cosurfactant concentrations were utilised to process a number of the formulation's series. The Drug was added into exactly measured amounts of oil in screw-capped vials and if required, melted in a water bath for proper mixing. Then surfactant and cosurfactant were added to the oily mixture using a positive displacement pipette and stirred with a vortex to form a homogenous solution.[47]

2. **Preparation of Solid SNEDDS:**

   For the preparation of Self Nanoemulsifying Drug Delivery System (SNEDDS), it is the second-most important approach. There are several methods available for converting conventional liquid SNEDDS into solids, including high pressure homogenization, rotary evaporation, melt granulation, spray drying, spray cooling, and adsorption to solid carriers. But the adsorption procedure is simple and easy. It just involves the dropwise addition of selected liquid SNEDDS (L-SNEDDS) onto the appropriate adsorbents like Neusillin and thoroughly mixed with glass rod to produce the solid SNEDDS. The damp product that obtained was then passed through sieve no. 120 and dried at room temperature.[47]

Figure 2. Diagrammatic presentation of preparation of SNEDDS



Methods of Preparation:

1. **High pressure homogenizer:**

   It is one of the essential instrument for formulating and detecting nanoemulsions. This procedure involves applying high pressure to a system that includes an oil phase, an aqueous phase, and a surfactant or co-surfactant. With the use of a homogenizer, pressure is applied. Several factors, including hydraulic shear, severe turbulence, and cavitation, combine during this process to produce nanoemulsions with very tiny droplet sizes. The homogenizer valve produces severe turbulent eddies that are the same size as the mean diameter droplet (MDD) due to the high velocity of the mixture, which provides the liquid significant energy. Droplet size decreased because they were separated from eddy currents. Simultaneously, the pressure decrease over the valve, cavitation takes place and creates additional eddies disruption droplets. By reducing the gap size, the droplet's pressure eventually rises, causing cavitation occur to a greater extent.[46]

Surface tension can be reduced more by surfactant mixtures than by their individual components. The surfactant should, wherever feasible, be dissolved in the dispersed phase instead of to the continuous phase, which frequently results in tiny droplets. A few issues with homogenizers include low productivity and component damage as a result of excessive heat generation. This technique can only be used for preparing liquid oil in water (O/W) nanoemulsions with less than 20% oil phase and it cannot produce cream nanoemulsions with high viscosities or hardnesses and mean droplet diameters below 200 nm.[48]

2. **Micro fluidization:**

   The "MICROFLUIDIZER" is a device used in microfluidization technology. The product is forced into the interaction chamber, which is made up of tiny channels called micro channels, by use of a high pressure positive displacement pump (500–2000 PSI).[49] Very small particles in the submicron range are produced as a result of the product flowing via microchannels and impinging on a impingement region. An inline homogenizer is used to blend the two solutions (the aqueous phase and the oily phase) and turn them into a coarse emulsion. The coarse emulsion is introduced into a microfluidizer for further processing to create a stable nanoemulsion. Until the desired particle size is achieved, the coarse emulsion is repeatedly passed through the interaction chamber microfluidizer. A homogenous, clear, stable nanoemulsion is produced by filtering the bulk emulsion under nitrogen to eliminate large droplets.[50]

3. **Sonication method:**

   The sonication mechanism is used in the sonication method to reduce the droplet sizes of conventional emulsions or microemulsions. Only small batches of nanoemulsion may be made by this process, which is helpful for determining the size of droplets but is not appropriate for large quantities.[48]

4. **Phase inversion method:**

   For the manufacturing of nanoemulsion and microemulsion, the phase inversion approach is important. The approach is based on the temperature response. Chemical energy from phase transitions that occur during emulsification processes is used to produce fine dispersions. Changing the composition at a constant temperature or the temperature at a constant composition results in the proper phase transitions. These techniques work by modifying spontaneous emulsion formation. By changing the system's temperature, it is possible to force a shift from an o/w nanoemulsion formed

at low temperature to a w/o nanoemulsion formed at higher temperature, which results in the spontaneous emulsion formation of a nonionic surfactant.[51]

5. **Pseudoternary phase diagram:**

The determination of the self-nano emulsifying drug delivery system (SNEDDS) is mainly depends on the pseudoternary phase diagram which is created using water titration process. It is a diagram representing the relationship between the oil, water and s-mix i.e. surfactant and co-surfactant mixture. The process involves the preparation of solutions with various weight ratios of surfactant to co-surfactant and oil, such as 1:1, 2:1, 3:1 and so on, these solutions are then vortexed for five minutes to produce an isotropic mixture. Following that, each combination was titrated with water and visually inspected for phase clarity and flowability. The weight measurements were used to determine the water concentration at which the changes from turbidity to transparency or transparency to turbidity took place. After that, these values were applied to determine the borders of the microemulsion domains that corresponded to the selected value of the oils as well as the (S/Co S) mixing ratio. Phase diagrams have also been created to assess the impact of drug addition on the microemulsion boundary when a drug had been added using drug enriched oil as the hydrophobic component. Then phase diagrams were constructed using proper software.

This diagram's corner may be considered as 100% concentration of each phase's content. [52][53]

Characterization of self nano emulsifying drug delivery system (SNEDDS):

1. **Morphological Study**: Morphological analysis is essential because it tells us characteristics like the formulation's colour, smell, consistency, density, and appearance. The self-Nano emulsifying drug delivery system (SNEDDS) has been utilised to study globules under the transmission electron microscope (TEM). Globules in the self-Nano emulsifying drug delivery system (SNEDDS) have been examined using a transmission electron microscope (TEM).[54]
2. **Thermodynamic Stability Studies:** A lipid-based formulation's physical stability is crucial for performance, which might be impacted by drug precipitation in the excipient matrix. Additionally, improper formulation Physical stability can cause excipient phase separation, which has an impact on formulation performance as well as visual appearance.

Additionally, incompatibilities between the formulation and as a result, the gelatin capsule shell might lead to brittleness or deformation, delayed disintegration, or insufficient drug release.[55][56]

The thermodynamic stability studies were performed for SNEDDS formulation in three steps:

a. **Heating cooling cycle:** The study examined six cycles with storage periods of at least 48 hours at each temperature, ranging in temperature from 4°C to 45°C. The formulations that withstand these temperatures, centrifugation tests are conducted.[57]

b. **Centrifugation:** Using a laboratory centrifuge, the formulations were centrifuged for 30 minutes at 5000 rpm. Phase separation and creaming or cracking issues, as well as other instability issues, were investigated in the resulting formulations. For further investigation, the formulations that are stable are chosen.[57]

c. **Freeze thaw cycle:** By using freeze thawing, the stability of SNEDDS was evaluated. The formulations go through three rounds of freezing at 4°C for 24 hours and thawing for 24 hours at 40 °C. Centrifugation was carried out at 3000 RPM for 5 minutes. The preparations were then checked for phase separation. If phase separation, creaming, or cracking were not observed in the formulations then formulation passed this test, indicating high stability.[58]

3. **Dispersibility Test:** The efficacy of self-emulsification of oral nano or microemulsions is assessed using a standard USP XXII dissolving apparatus II. One millilitre of each formulation was added to 900 mL of distilled water at a temperature of 37.5°C. A standard stainless steel dissolving paddle moving at 50 rpm provided the gentle agitation. The in-vitro performance of the formulation has been graded using the following scale.[54]

4. **Turbidimetric Evaluation:** Nepheloturbidimetric analysis is used for monitoring the development of the emulsification process. After a given amount of Self emulsifying system was mixed with a fixed amount of suitable medium (0.1N HCL), the rise in turbidity was measured using a turbid-meter under continuous stirring (50 rpm) on a magnetic plate at ambient temperature. When the total duration of time needed for full emulsification is too short, it is impossible to monitor the rate of change in turbidity.[58]

5. **Percent Transmittance:** The system's % transmittance is calculated at a particular wavelength using a UV spectrophotometer and respected solvent is used as a blank. If a formulation is transparent, its percent transmittance will be more than 99 percent. For each sample three replicate assays were performed.[59]
6. **Droplet Size Analysis Particle Size Measurements:** The droplet size of the emulsions is measured using a Zeta sizer 1000 HS that can measure sizes between 10 and 5000 nm and photon correlation spectroscopy, which investigates variations in light scattering caused by Brownian motion of the particles. After external standardisation using spherical polystyrene beads, light scattering is measured at 25°C at a 90° angle. The fact that the particle's nanometric size range remains constant even after being diluted with water 100 times indicates that the system is compatible with excess water.[55]
7. **Viscosity Determination:** Generally, capsules made of either soft gelatin or hard gelatin are used to deliver the SEDDS system. Because of this, it's typically simple to pour into capsules, and this system shouldn't be too thick to have become an issue. The rheological characteristics of the nanoemulsion are evaluated using a Brookfield viscometer.[60] Whether the system is water/oil or oil/water is determined by the viscosities. When a system has low viscosity, it is an o/w kind of system, and when it has high viscosities, it is a w/o type of system.[61]
8. **Drug Content:** Nanoemulsion containing a dose of drug equivalent to 10 mg was dissolved in methanol and measured by using a UV spectrophotometer at respective wavelength of drug.[57]

9. **Robustness to dilution:** By diluting 50 mg of SNEDDS to 50 ml with different dissolving media, including water and phosphate buffers (pH 1.2, 6.8, and 7.4), the effect of dilution was assessed. The diluted formulations were kept and observed after 12hr for any signs of phase separation or drug precipitation.[61]
10. **In *vitro* Dissolution:** The USP type II dissolution apparatus is used to conduct quantitative in vitro dissolution studies to evaluate drug release from oil phase into aqueous phase using 500 ml of simulated gastric juice containing 0.5% w/v of SLS at 50 rpm and keeping the temperature at 37±0.5ºC. At regular intervals, aliquots of samples are taken out and the removed volume is replenished with fresh media. After sample collection, samples are examined using a UV spectrophotometer or another appropriate method.[14]

Application

1. **Improving Water Solubility of Poorly Water-Soluble Drug**

   The Self-Nanoemulsifying Drug Delivery System (SNEDDS) is essential to enhanced water solubility of poorly water-soluble drugs mainly BCS class I and class II drugs and enhances their oral bioavailability.[8]

2. **Applications of SNEDDS in Drug Delivery**

   Nanoemulsions (SNEDDS) have been used in various types of drug delivery systems, including cosmetics and transdermal drug delivery, cancer therapy, vaccine delivery, cell culture technology, formulations are important for increasing oral delivery of poorly soluble drugs, ocular and otic drug delivery systems, parenteral drug delivery, and pulmonary drug delivery systems, as well as intranasal drug delivery system.

3. **Protection Against Biodegradation**

   SNEDDS are important for the delivery of macromolecules such peptides, hormones, enzyme substrates and inhibitors and these are protected from enzymatic degradation.[62]

Conclusion

The most recent developments in SNEDDS research have been carefully examined in order to increase the oral bioavailability and solubility of therapeutic drugs with poor water solubility. For BCS class II and IV compounds with low water solubility, it is a promising strategy. One of the most significant benefits that distinguishes SNEDDS apart from other novel drug delivery systems is its ease of production and scale-up because it requires only extremely basic and cheap manufacturing facilities. when liquid SNEDDS were converted to solid SNEDDS, the rate of drug degradation was decreased but not completely eliminated. An isotropic mixture of oils, surfactants, co-surfactants (Smix), and/or co-solvents is called a self-nanoemulsifying drug delivery system (SNEDDS). It spontaneously forms a fine o/w Nanoemulsion with little agitation in the aqueous phase. SNEDDS is an excellent substitute for the formulation of drugs which are not easily soluble in water. Due to the increased surface area on the dispersion and drug molecule absorption rate, SNEDDS improves drug dissolution. The oral delivery of lipophilic medicines, which is frequently made possible by SNEDDS, is crucial for enhancing oral bioavailability. Despite the fact that there is a lot of research being done in this field, additional factors like in vitro/in vivo relationship need to be demonstrated.

Future perspective

In the last ten years, SNEDDS technology research has grown significantly in relevance, and several papers on various SNEDDS formulations have been published in the literature. In particular for the poor solubility medicines, SNEDDS have predominantly been investigated for improving bioavailability in oral administration of drugs. Drugs in SNEDDS have been studied for pH-catalyzed and solution-state degradation. Drug degradation can be decreased by converting SNEDDS to a solid state; this has been proved and improved. In order to increase the stability of pH-sensitive medications, it is essential to discover microenvironment-modulation techniques. There are several ways to convert liquid SNEDDS into solid dosage forms like tablets and pellets. However, it is necessary to find a suitable highly porous amphiphilic carrier that can turn liquid SNEDDS into a solid powder without significantly increasing the volume or bulk density. The potential applications of SNEDDS in delivery methods other than the oral route may be still explored but still there are several additional dosage forms that need to be developed in the form of SNEDDS, which are primarily useful in improving the solubility of drugs. The capacity of drug delivery experts to deal with these SNEDDS aspects will determine if the technology can be made commercially available.

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