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Review Article

A REVIEW ON SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEMS (SNEDDS)

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ABSTRACT

Lipid based drug delivery formulations have been widely reported in the literature for improving drug solubility, permeability and bioavailability. The systems involve simple oil solutions, multiple, dry and coarse emulsions, nano, micro emulsifying systems and complex emulsifying drug delivery systems. Self-emulsifying systems are further classified as-SNEDDS, SMEDDS which are widely prevailing and commercially viable oil-based approach for those drugs which exhibit low rate of dissolution and inadequate absorption. Since development of SNEDDS, researchers drew interest in this field to deal with challenges of poorly hydrophilic drugs. SNEDDS is an established method for increasing solubility and bioavailability of lipophilic compounds. Due to their large scale production and robustness of SNEDDS, they show improved patient compliance with high drug loading capacity. The presence of biocompatible and biodegradable ingredients along with drug targeting opportunities allow SNEDDS to be used in solubility enhancement techniques. In this article, an attempt was made to give an overview of SNEDDS, formulation excipients, mechanism along with recent advancements, their advantages, disadvantages, applications and future perspectives.

INTRODUCTION

In recent era, the design of poorly soluble complexes posed challenges for formulation in pharmaceutical industry. Up to 40% of newer chemical entities developed by the pharmaceutical industry are sparingly soluble or lipophilic compounds, that leads to poor oral bioavailability, high inter and intra subject variability and lack of dosage regimen[(1)].

Self-nanoemulsifying drug delivery systems (SNEDDS) are considered as nano emulsion as anhydrous forms or preconcentrates of the nano emulsion. Self-nanoemulsifying Drug Delivery system (SNEDDS) is an isotropic combination of the synthetic or natural oil, surfactants, co-surfactants and, on the other hand, aqueous media consists of one or more hydrophilic solvents and co-solvents/surfactant's capacity to generate fine oil-in-water (O/W) type nano-emulsions inslight agitation environment[(2)]. The globules size range in the SNEDDS is below 100nm when dispersed in water. Current studies on Self-Nano emulsifying Drug Delivery System (SNEDDS), is working on enhancement of aqueous solubility of BCS Class II and Class IV drugs which are sparingly water-soluble in nature[(3).]

Using non-ionic surfactant and medium chain tri glycerides oils the SNEDDS were formulated as its oral ingestion is critical[(4)]. To overcome the dissolution barrier and to enhance reproducibility of plasma drug concentration and absorption rate, the drug is formulated as SNEDDS [(5)].

SMEDDS are formulations, which produce a transparent microemulsion of water-in-oil or oil-in-water with a diameter of < 250 nm. SNEDDS have a droplet size of 20 to 200 nm that is translucent and thermodynamically stable[(6)]. SNEDDS is a competent, well-designed, and patient compliant technique for sparingly soluble drugs, as it enhances the solubility and permeability, enhances absorption and dissolution patterns in the GI tract[(7)].

Drug selection criteria for SNEDDS

The SNEDDS system is a novel approach to enhance oral bioavailability of drugs that are poorly water-soluble drugs. in the Biopharmaceutical classification system (BCS) can categorize into four classes, comparison to class i and class iii drugs, class ii and class iv drugs have lower aqueous solubility[(9)]. Under the self-nanoemulsifying drug delivery system, class ii and class iv drugs can increase their aqueous solubility and oral bioavailability. the SNEDDS is important to prevent problem of enzymatic degradation associated to class i drugs and class iii drugs and improved solubility and bioavailability [(10)]. based on the solubility and permeability analysis a schematic representation about biopharmaceutical classification system (BCS) having four classes of system.

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Lipidized forms of class ii and class iv drugs enhance their absorption by bypassing the barrier of reduced water insoluble solubility and illustrate their dissolution in GI through membrane transfer to the bile-salt mixed micellar phase. through which absorption happens readily[11]. This regard, the properties of the drug, including water solubility, log P, do not provide sufficient insight into the suitability of a lipid-based formulation as they cannot predict the vivo effects[12].

Mechanism of self-emulsification

In accordance with Reiss theory, Self-emulsification happens when alteration in entropy favors dispersion which is higher than the energy essential to increase the surface area of the distribution. The free energy of traditional emulsion is a direct mechanism of energy required to generate a new surface between water and oil phases.

This is described as

$$\Delta G = \Sigma N\pi r2\sigma$$

Where
ΔG = free energy associated with the process,
N = number of droplets,
r = radius of droplets,
σ = interfacial energy.

The oil and water phases of emulsion incline to separate with period to decrease the interfacial area and next, the emulsion is stabilized using emulsifying agents, which produce droplets of emulsion monolayer and thereby reducing the interfacial energy as well as providing a barrier to avoid coalescence. To attain spontaneous emulsification, which is related with a reduction of the phase inversion temperature, the specificity of surfactant combination is essential and thereby increasing the ease of emulsion[13].

Factors affecting SNEDDS[14]:

- The capacity of SNEDDS to uphold the drug in solubilized form is predisposed by the drug solubility in oil phase.
- If surfactant or co-surfactants contributeto a larger extent for drug solubilization, then there can be a precipitation risk, as dilution of SNEDDS will allow in lowering of solvent capability of surfactant or co-surfactant.
- SNEDDS are not suitable candidates for drugs which are administered at high doses.
- If drug's solubility is limited to both water and lipids, they are not suitable for formulation into SNEDDS.
- The ability of SNEDDS to keep the drug in a solubilized state is greatly influenced in oil phase.

Advantages of SNEDDS

- They have high drug payload.
- SNEDDS achieve controlled drug distribution profile.
- In relation to surface interfacial area, SNEDDS enable for better drug partition among water and oil phase[15].
- SNEDDS enhance the pharmacokinetics of the drug administered, which decrease the dosage frequency [16]
- SNEDDS are highly stable preparations and involve simple manufacturing techniques.
- The drug is sheltered from the aggressive atmosphere in GI tract by SNEDDS.
- SNEDDS increase the extent and of rate drug absorption.
- SNEDDS permit the selective drug aiming towards accurate absorption window in GI tract[17].

Disadvantages of SNEDDS

a. For strength assessment, SNEDDS in vitro models need more research and validation.
b. Lower drug stability and incompatibility.
c. Drugs' chemical insecurities.
d. Conventional dissolving procedures are unsuccessful for SNEDDS, as they depend on digestion prior to disintegration[18].
e. Additional research into the in vitro-in vivo correlations of SNEDDS is required.
f. Likelihood of precipitation and drug leakage[19].
g. High making cost.

Composition of Snedds

SNEDDS are composed of following components:
Drugs,
Oil,
Surfactant,
Co-surfactant,
Co-solvents[20].

Drugs

SNEDDs are often preferred for drugs which have a poor water solubility. In most cases, BCS class II and class IV drugs are frequently used in production of SNEDDS [21]. Physicochemicalfeatures of the drug, such as weight, pKa, molecular structure, quantity, and presence of ionizable groups, log P all have a crucial impact on SNEDDS performance19. Lipophilic drugs exhibiting log P values greater than 5, are suitable candidates for SNEDDS[22].

Class II Drugs	Class IV Drugs
Griseofulvin	Nelfinavir
Ibuprofen	Indinavir
Haloperidol	Mesylate
Carbamazepine	Azathioprine
Folic Acid	Acetazolamide
Dapsone	Albendazole

Oil

The oil phase takes great rank in the preparation of SNEDDS as physicochemical features of oil such as, viscosity, polarity and molecular volume significantly rule the spontaneity of the nano emulsification procedure, drug solubility of nano emulsion and droplet size influence the biological destiny of nano emulsions, it's mainly associated with O/W nano emulsion. The oil is fundamental for maximum solubilizing capability for selected drug candidate in oil phase. The size of nano emulsion is directly proportional to the hydrophobicity of the oil and concentration of oil phase in SNEDDS [23].

In specific cases, using a mixture of oils is also used to meet ideal properties of the oil phase. For microemulsions and nanoemulsions, a parallel concept has been used. For example, a mixture of medium-chain triglyceride and fixed oilis used in specific cases to have a balance between loading dose and emulsification. Due to their lack of ability, to solubilize greater drug concentrations, edible oils are not involved in the SNEDDS design. Due to the innovation of improved emulsification procedures with more surfactants suitable for oral administration, hydrolysed vegetable oils are employed[24].

Oil	Drug
Lemon oil	Diclofenac Sodium
Palm kernel oil	Ibuprofen
Captex 500	Furosemide
Castor oil	Cyclosporin-A
Capmul MCM C8	Glibenclamide

Surfactants

They are well-defined as molecules and ions that are adsorbed at interface. It can avoid interfacial tension and arrange interfacial area. The choice of surfactant is critical for the preparation of SNEDDS. Surfactant features such as viscosity and affinity for oil phase, hydrophilic-lipophilic balance (in oil), cloud point, have a great impact on nano emulsification procedure [(25)].

The concentration of surfactant in SNEDDS formulation has significant influence on the droplet size of nano emulsions. The suitability of selected surfactant for the required route of administration is to be considered during surfactant choice[(26)].

Classification Surfactant Molecule

The four main groups of surfactants are[(27)]:
Anionic surfactants
Cationic surfactants.
Non-ionic surfactants.
Ampholytic surfactants

Anionic surfactants

The hydrophilic head or group of an ionic surfactant carries a net charge. If the charge is negative, it is called anionic surfactant. Commonly used one's are soybean phospholipids(lecithin), carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3-), potassium laurate, sodium lauryl sulphate, fatty acid soaps, sodium lauryl sulfate, sodium laureth, polyoxyethylene ether sulfate.

Cationic surfactants

The hydrophilic head or group of an ionic surfactant carries a net charge. If the charge is positive, it is called cationic surfactant. They are mainly primary, secondary, tertiary amines and quaternary ammonium salts of higher alkyl groups such as C12-14 alkyldimethylbenzyl ammonium chloride, octadecyl trimethyl ammonium chloride.

Non-ionic surfactants

When hydrophilic group has zero charge, but when it has strong polar functional groups such as polyoxyethylene or hydroxyl group, which shows water solubility. Sorbitan esters (Spans) and polysorbates (Tween 20) are good examples. Non-ionic surfactant molecules are more stable when compared to ionic molecules, and they are thermodynamically stable and nontoxic molecules with a rationally high hydrophilic lipophilic balance (HLB) to produce stable SNEDDs. 30-60% surfactant concentration is used to form stable SNEDDs[(28)].

Ampholytic surfactants / Zwitterionic surfactants

The surfactant unit comprise of positive as well as negative charge.
Sulfobetaines are good instance.

Co-surfactant

It is analogous to surfactant unit. Co-surfactant was added along with surfactant or mixture of surfactants to enhance the ability of surfactant to increase hydrophilicity of poorly water-soluble drugs. The significant role of co-surfactant in SNEDDS is minimization of oil-water interface and offer larger surface area and permit the spontaneous formation of nano emulsion. The SNEDDS preparations require high surfactant concentrations (> 30% w/w), which can be reduced with the addition of a co-surfactant[(29)]. These, in blend with surfactants, decrease the interfacial tension to a negative value, at the point which it expands to produce fine droplets, that are later adsorbed with high quantities of surfactant and surfactant/cosurfactant till, interfacial tension yieldspositive value. This method is called "spontaneous emulsification." Examples are hexanol, octanol and pentanol are hydrophilic co-surfactants which reduce the interface among oil and water[(30)].

Co-solvents

Basically, an effective self-emulsifying preparation, requires a high surfactant concentration. Accordingly, co-solvents such as propylene glycol, ethanol and polyethylene glycol are essential to facilitate the dissolution of more quantities of water-soluble surfactant. These co-solvents play the role of the co-surfactant with in the microemulsion system. On the other hand, alcohol and additional volatile co-solvents have the disadvantage of evaporating into the hard and soft gelatin capsules shell, resulting in drug precipitation[(31)].

Polymers

An inert polymer matrix that characterises 5 to 40% composition of relative weight, is non-ionizable at physiological pH, and forms a matrix. Ethyl cellulose and Hydroxyl propyl methyl cellulose are two examples of surfactants[(32)].

Methods for Preparation Snedds

High energy approach

By using this approach, nano emulsion is formulated which is based on the blend composition, that comprises surfactant, co-surfactant, cosolvents, and other functional groups, and energy is used in preparation of mixture compound. The emulsion is mechanically treated to become a nano emulsion[(33)].

Sonication Method

This process is crucial for estimating the droplet size and for decreasing the droplet size in a conventional emulsion formulation using a sonication apparatus. It can be used on small batches of nano emulsion[(34)].

High Pressure Homogenizer

Among the most significant tools for detecting and making nano emulsions is the high-pressure homogenizer. Under high-pressure circumstances, the oil in water surfactant mixture was pumped by resistive valve. The high shear stress is accountable for the development of very fine emulsion droplets. The droplet size decrease during homogenization is described by a combination of two theories: cavitation and turbulence[(35)]. The high velocity of resulting mixture gives the liquid a share of energy, which reasons to severe turbulent eddies and same mass as the mean droplet diameter (MDD)

within the homogenizer valve. Droplets were sideways from eddie currents resulting in a decrease in droplet size. In the equivalent time, the pressure around the valve drops and cavitation follows, and more eddies and droplets breakdown. By lowering the gap size, the pressure of the droplet is raised, leading toelevated degree of cavitation. Emulsion droplets with diameters lower than 100 nm are commonly produced[36].

Micro fluidization

It is a critical tool for identifying and makingnanoemulsion. A machine known as a "Micro Fluidizer" is utilized in this technique. This type of tool is utilized in a high-pressure positive displacement pump (500- 300 PSI) that allows the product to pass through the interaction chamber. Micro channels are minor openings which are used in high-pressure positive displacement pumps. The product was passed through micro channels and imposed on impingement area, resulting in submicron sized particles. In the aligned homogenizer, two solutions of aqueous and oil phase systems are unitedand produced a coarse emulsion. The coarse emulsion is treated in a micro fluidizer and then additionally processed to produce a transparent, homogeneous, and stable nano emulsion[37].

Phase inversion Method

This method is useful for preparation of nano emulsion and micro emulsion. The approach is based on temperature. Many physical variations occur during this approach, including particle size, physicochemical changes and in vivo - in vitro drug release rate. Modifying the spontaneous emulsion development is used in this technique. The temperature change can be achieved using non-ionic surfactant. A transition of o/w nano emulsion was designed at low temperature and w/o nano emulsion was designed at high temperature[38].

Evaluation Tests

Morphological Study

This study is significant, since it provides data about the formulation's exterior appearance, like odour, colour, density, consistency and look. The transmission electron microscope (TEM) was used to inspect globules in the self-Nano emulsifying drug delivery system (SNEDDS) [39].

Viscosity Determination

The SEDDS system is frequently administered in hard gelatin or soft gelatin capsules. As a result, it's regularly easy to pour into capsules, and the system shouldn't be too thick to trigger a problem. Brookfield viscometer was used to test the micro emulsion's rheological features. This viscosity determination corresponds, whether the system is oil/water or water/oil. If the system has minimal viscosity, then it's o/w type of the system and if it has high viscosity then it's w/o type of the system[40].

Stability Study

Stability studies are essential for determining the nano emulsion system's purity and quality. The tolerance of a preparation is determined by its stability. The stability of various nano emulsion preparations is evaluated by exposing them to mechanical stress circumstances (centrifugation at 2000-4000 rpm) and keeping them at various temperatures ranging from 4 ±1 °C to 40 ± 1 °C at various time breaks. The effect of mechanical stress conditions on physiochemical stability of the nano emulsion is measured by percent phase separation, anyphysical change or breaking of the nano emulsion. Later, 60 minutes of centrifugation at 2000 rpm, there was no detectable change in the preparations[41].

Dispersibility Test

A standard USP XXII dissolution apparatus 2 was used to assess the efficiency of self-emulsification microemulsions or oral nano emulsions. At 37± 0.5 °C, one millilitre of each preparation is added to 500 mL of water. Gentle agitation was done by a standard stainless steel dissolution paddle rotating at 50 rpm. The resulting grading system was used to visually judge the preparation's in vitro performance[42].

Freeze thaw cycle

The stability of SNEDDS isevaluated via freeze thawing. Three freeze-thaw rounds were performed on the preparationby freezing at 4°C for 24 hours followed by thawing at 40°C for 24 hours. For 5 minutes, centrifugation was completed at 3000 RPM. Next, the preparations were assessed for phase separation. The preparationswhich passed this test showed excellent stability, with no phase separation, cracking or creaming[43].

Turbidimetric Evaluation

The increase of emulsification is examined by nepheloturbidimetric analysis. Under a continuous stirring speed (50 rpm) on a magnetic plate at room temperature, the rise in turbidity is measured by using turbid meter, where a fixed quantity of self-emulsifying system is added to a fixed quantity of proper medium (0.1N HCL). It is not possible to monitor the rate of variationin turbidity, when the time involved for complete emulsification is very short (rate of emulsification)[44].

Droplet size and Polydispersity index (PDI): The size of droplet and PDI was calculated by using photoncorrelation spectroscopy system. The sample was dissolved in a suitable solvent to exact concentration and mixing was done to get the formulation[45].

In Vitro Diffusion Study

The study was performed by dialysis technique, where in vitro diffusion tests were carried out to assess the release behaviour of preparation from the liquid crystalline phase around the droplet.

Drug Content

The drug was extracted from a pre-weighed SEDDS by dissolving it in anappropriate solvent. The drug content present in solvent extract is compared to a standard drug solvent solution by employing a correct analytical technique.

Bioavailability Study

Based on the self-emulsification features, stability and particle size data of micro emulsion formulation is chosen for bioavailability studies. The in vivo study was performed to calculate the drug present after the administration of preparation. Pharmacokinetic parameters of the maximum plasma concentration (C_{max}) andso the drug's corresponding time (t_{max}) subsequently after oral administration is determined. The next equation to assess the relative

bioavailability of the SEDDS making wasmatched to the conventional tablet[46].

Relative Bioavailability (%) = (AUC test/AUC reference) X (Dose reference/Dose test).

Applications

Applications of Nanoemulsion in Drug Delivery

SNEDDS have been utilised in a wide variety of drug delivery systems, comprising cosmetics, vaccine delivery, transdermal drug delivery, cell culture technology, cancer therapy, ocular and optic drug delivery systems, parenteral drug delivery, intranasal drug delivery, pulmonary delivery of drugs and formulations are significant for improving oral delivery of poorly or sparingly soluble drugs [47].

Protection Against Biodegradation

SNEDDS, SEDDS, and SMEDDS, are crucial for delivering macromolecules such as hormones, peptides, enzyme substrates that are inhibitors that defend against enzymatic degradation[48].

Improving Water Solubility of Poorly Water-Soluble Drug

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is significant to improve water solubility of poorly hydrophilic drug and improves the oral bioavailability [49].

Enhancing Oral Delivery of Proteins

Peptides consists of high hydrophilicity, less stability in the GI tract and poor permeability to make them effective for oral delivery, SNEDDS demonstrate to be a better approach for enhancing the absorption of proteins[50].

Improved Oral Delivery of Natural Phytochemicals

Natural phytochemicals that are confirmed to be potential against hepatitis, cancer, arthritis and suffer from minimal water solubility and depressed metabolic stability. SNEDDS showed to be areplacement method for such phytochemicals for better bioavailability, therapeutic efficiency of several phytochemicals, including carotenoids, triterpenoids, alkaloids and hepatoprotective agents[51].

Protection against Biodegradation

The potentiality of SNEDDS to weaken drug degradation and improve drug absorption is strategic for drugs with minimal bioavailability. Most drugs experience degradation in the body because of acidity in stomach, hydrolytic degradation, and enzymatic degradation. These drugs can be shielded by incorporating into SNEDDS, that act as a barrier among the degrading conditions and drug. Drugs, like aspirin, experience hydrolysis to salicylic acid in GI tract, and thus, degrading[52].

Future Perspective

The innovations in SNEDDS research in the recent years was discovered intensively for development of oral bioavailability and solubility of class II and class IV drugs. The preparation of liquid SNEDDS to a solid SNEDDS helps to degrade the drug degradation rate but cannot eliminate it completely. Consequently, it is significant to recognize microenvironment modulation systems for enhancing the strength of pH-sensitive drugs. The pH catalysed and solution-state degradation of preparations in SNEDDS is to be analysed. Significant research is achieved for the transformation of liquid SNEDDS to a solid SNEDDS including tablets and pellets. Here exists a requirement to identify anappropriate porous amphiphilic carrier for renovating of liquid SNEDDS into a solid powder without a foremost rise in density and volume. The commercialization of SNEDDS depends on capability of drug delivery, scientists to focuson this feature of SNEDDS.

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