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SNEDDS: A VITAL ROLE IN DRUG DELIVERY TRUE OR MYTH

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ABSTRACT

Nanoemulsion drug delivery system is extensively reported within the literature for the enhancing drug solubility, permeability, and bioavailability. A considerable majority of novel pharmacologically active constituents produced in recent drug discovery programs are lipophilic and poorly soluble, posing a significant problem for pharmaceutical researchers enhancing the oral bioavailability of such drug molecules. Self-nano emulsifying drug delivery systems (SNEDDS), are the viable oil-based approaches for drugs that exhibit low dissolution rate and inadequate absorption. Ever since the progress of SNEDDS, researchers have been focusing on the challenges of BCS Class II and Class IV Drugs for enhancing water Solubility of poorly water-soluble drugs. SNEDDS is a Validate method for enhancing the solubility and bioavailability of lipophilic compounds. It's the isotropic mixture of oil, surfactant, co-surfactant molecules and it also containing co-solvent molecule. which spontaneously form oil-in-water nano emulsion of approximately 200 nm or less in size upon dilution with water under gentle stirring. It's Drug delivery system Which possess thermodynamically and kinetically stability. The physicochemical properties, drug solubilization capacity considerably regulates the selection of the SNEDDS components. The present review describes Preparation, components, mechanism of self-Nano emulsification, biopharmaceutical aspects, characterization methods and applications of Selfnanoemulsifying drug delivery system (SNEDDS).

KEYWORDS: Nano-emulsion, Poor bioavailability, Self-emulsifying drug delivery system, SNEDDS surfactant, co-surfactant, Pseudo ternary phase diagram, In-vitro dissolution etc.

INTRODUCTION

Nanoemulsions are dispersions of shear-induced ruptured nanoscale droplets. It can be defined as oil-in-water (o/w) emulsions with mean droplet diameters ranging from 50 to

1000nm. It is very likely that nanoemulsions played commercially important role; since they can typically formulate using significantly less surfactant than is required for nanostructured lyotropic microemulsion phases. Nanoemulsions are kinetically stable, even for several years. The term sub–micron emulsion (SME), mini-emulsion and ultra-fine emulsion are used as synonyms. It has to be considered that these novel nanoemulsions again are fluid systems where the production is not easy to handle. Lipophilic drug entrapped lipid nanoemulsions improved bioavailability of drugs by increasing drug absorption through the gastrointestinal tract.

Self-emulsifying drug delivery system is one of the effective systems in addressing solubility issues. Self nanoemulsifying drug delivery system (SNEDDS) is composed of an isotropic mixture of oil, surfactant, co-surfactant and drug. Upon ingestion, this isotropic mixture will come in contact with the aqueous phase of gastrointestinal tracts and form an oil-in-water emulsion at a nanoscale range with the aid of gastrointestinal motility. This stable emulsion can provide a large interfacial area for partitioning of drug between oil and aqueous phase and potentially offer better dissolution rate and improved bioavailability. SNEDDS appears to be an attractive choice of formulation as it requires simple and cost-effective manufacturing facilities. This is because SNEDDS is a physically stable lipid solution and it omits the need of high energy emulsification process, and thus reduces the manufacturing cost. In addition, better dissolution rate and more predictable bioavailability of SNEDDS imply the reduction in drug dose and possibly eliminate the dose-related side effects.[1,2] SNEDDS are generally encapsulated either in hard or soft gelatin capsules. SNEDDS may interact with the capsule resulting in either brittleness or softness of the shell. To overcome this problem SNEDDS need to convert into Solid SNEDDS. Many techniques are offered to convert conventional liquid SNEDDS to solid such as adsorption to solid carriers, spray drying, spray cooling, and melt granulation, rotary evaporation, freeze drying and high pressure homogenization. But adsorption process is simple and involves simply addition of the liquid formulation to solid carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or mixed with suitable excipients before compression into tablets.[3,4]

TYPES OF NANOEMULSION (SNEDDS)

Water in oil (W/O)

Nanoemulsion In Which Droplet of Water was dispersed in Continuous Phase oil.[5,6]

Oil in water (O/W)

Nanoemulsion In Which Oil droplet was dispersed in Continuous Phase Water.[5,6]

Bi-continuous Nanoemulsion

In which Surfactant was Soluble in Both Oil as well as water Phase, and droplet was dispersed in both Oil as well as water phase.[7]

Selection of Appropriate Drug Candidates for SNEDDS[8-12]

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. 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. Based on the solubility and permeability analysis a schematic Representation about Biopharmaceutical Classification System (BCS) having four classes of system which is shown in Figure No.1.

Figure 1: BCS Classification.

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. 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.

Advantage of Snedds[13,14]

• SNEDDS enhance the bioavailability of the drug, thus, reducing dosage frequency
• SNEDDS enable selective drug targeting towards precise absorption window in GI tract
• They possess higher drug payload
• SNEDDS manage controlled drug delivery profile
• SNEDDS are highly stable for mu lat ion a nd uncomplicated manufacture techniques
• SNEDDS facilitate a larger surface interfacial area for drug partitioning among oil and water
• SNEDDS facilitated wider drug distribution in the stomach and GI tract, thus, reducing the irritation caused by extensive contact among drug and gut walls
• SNEDDS protect the drug from the aggressive environment in the GI tract
• SNEDDS improve the rate and extent of absorption

Disadvantages of Snedds[13,15]

• The conventional dissolution techniques cannot be applied for SNEDDS as they are dependent on digestion former to dissolution
• The in vitro models of SNEDDS need further research and validation for strength evaluation
• The in vitro-in vivo correlations of SNEDDS must be studied further
• The chemical instability of drugs
• Higher amounts of surfactant used for formulation (30–60%)
• Higher production cost
• Lower drug incompatibility and stability
• Possibility of drug leakage and precipitation

Table 1: Comparision between SMEDDS and SNEDDS.[5]

S.NO	SMEDDS	SNEDDS	Ref No.
1	It is Self-Micro emulsifying drug delivery system	It is Self-Nano emulsifying drug delivery system	[16]
2	It is turbid in nature	Less energy required for preparation	[17]
3	Large amount of energy is required for preparation as compare to nanoemulsion	Less energy required for preparation	[18]
4	Droplet size is 100-300nm	Droplet size is less than 100nm	[19]

5	It is thermodynamically stable	It is thermodynamically and kinetically stable	[20]
6	It is optimized by ternary phase diagram	It is optimized by Psedoternary phase diagram	[21]

COMPOSITION Of SNEDDS[5]

- Oil,
- Surfactant,
- Co-surfactant,

Oil

The oil phase has great importance in the formulation of SNEDDS as physicochemical properties of oil such as molecular volume, polarity and viscosity significantly govern the spontaneity of the nano emulsification process, droplet size of the Nano emulsion, drug solubility and biological fate of Nano emulsions., it's mainly related to O/W nano emulsion. The oil is crucial for maximum solubilizing ability for selected drug candidate is important for selection of oily phase for Nanoemulsion Formulation. This is often most important approach having the high drug loading ability. The naturally also as synthetically occurring the mixture of oils and fats are triglycerides contain in long chain fatty acids in order to decrease the degree of unsaturation and is important to prevent oxidative degradation.[22] The nano emulsion size is directly proportional to the lipophilicity of the oil and concentration of oily phase in SNEDDS. Investigations by Anton and Vandamme and Sadurni[23], support the aforementioned statement. Interestingly, Long-chain triglycerides, in contrast to medium-chain tri-, di-, and mono-glycerides, have demonstrated a greater ability to enhance lymphatic transport of drugs (responsible for preventing first-pass metabolism of drugs)[24], whereas medium-chain mono- and di-glycerides have greater solubilization potential for hydrophobic drugs and permeation-enhancing properties.[25] Hence, it's going to be difficult for single oily component to possess optimum properties with reference to nano emulsification and drug delivery. In certain cases, employing a mixture of oils also can be used to meet optimum properties of the oily phase. For nanoemulsions and microemulsions an analogous concept has been utilized. For instance, a mixture of fixed oil and medium-chain triglyceride is used in certain cases to have good balance between drug loading and emulsification.[26] Due to their inability to solubilize higher drug concentrations, edible oils are not included in the SNEDDS formulation. Due to the creation of improved emulsification systems with more surfactants acceptable for oral administration, hydrolyzed vegetable oils are used. They

propose formulation and physiological remuneration. Medium-chain semi-synthetic chemicals, referred to as amphiphilic compounds that possess surfactant characteristics, are substituting the oils in SNEDDS.[27]

Surfactants

Surfactant are defined as molecules and ions are adsorbed at interface. It's having ability to prevent the interfacial tension and provide interfacial area. The selection of surfactant is additionally critical for the formulation of SNEDDS. Surfactant properties such as hydrophiliclipophilic balance (in oil), cloud point, viscosity, and affinity for the oily phase have a significant impact on the nanoemulsification process, self-nanoemulsification region, and hence nanoemulsion droplet size.[28] The concentration of the surfactant with in the SNEDDS has considerable influence on the droplet size of nanoemulsions.[29] The acceptability of the elected surfactant for the desired route of administration and its regulatory status must also be considered during surfactant selection.

CLASSIFICATION SURFACTANT MOLECULE

The four main groups of surfactants are[30]: -

- Cationic surfactants
- Anionic surfactants
- Ampholytic surfactants
- Non-ionic surfactants

Cationic surfactants

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

Anionic Surfactants

The hydrophilic group or head of an ionic surfactant carry a net charge. If the charge is negative, the surfactant is called anionic surfactant. Anionic Surfactant commonly fatty acid soaps, sodium lauryl sulfate, sodium laureth polyoxyethylene ether sulfate, sodium cetyl polyoxyethylene ether phosphate, soybean phospholipids(lecithin), carboxyl (RCOO-), sulphonate (RSO3 -) or sulphate (ROSO3-). Potassium laurate, sodium lauryl sulphate.

Ampholytic surfactants / Zwitterionic surfactants

The surfactant unit consist of both charges Positive also as negative Charge. Sulfobetaines are good example.

Non-ionic surfactants

The hydrophilic group has no charge, but it can contain strong polar functional groups like hydroxyl or polyoxyethylene, which gives it water solubility (OCH2CH2O). Sorbian esters (Spans) and polysorbates are good instances (Tween 20). Non-ionic surfactant molecules are more stable than ionic surfactant molecules, and they are nontoxic and thermodynamically stable molecules with a reasonably high hydrophilic lipophilic balance (HLB) to generate stable SNEDDs. 30-60% surfactant concentration is employed to form stable SNEDDS.[31] The SNEDDS formation causes with the higher surfactant and co-surfactant and oil ratios to the lipid mixtures of molecules and it is responsible for enhancement of oral bioavailability of poorly watersoluble Drugs. The surfactant concentration is mostly determined by the size of the droplet molecule used in the preparation of emulsification and Nano emulsification. This is often important for stabilization of oil Droplet under a part of surfactant system. The surfactant concentration is mainly depending on size of droplet the surfactant concentration was increases ultimately size of droplet was increases. It's important Component of preparation of Nanoemulsion system for improving the solubility of poorly water soluble drugs.[32]

Co-surfactant

It is similar function to surfactant unit. Co-surfactant was added alongside surfactant unit or combination of surfactant unit in order to capable to increases the ability of the Surfactant to improving water solubility of poorly water-soluble drug. The most important role of co-surfactant in SNEDDS is reduction of oil-water interface and provide the larger surface area and allow the spontaneous formation of nanoemulsion. The SNEDDS formulations require for higher surfactant concentrations (> 30% w/w), which can be condensed with the addition of a co-surfactant. These, in combination with surfactants, reduce the interfacial tension to a -ve value, at which point it expands to form fine droplets, which are then adsorbed with higher amounts of surfactant and surfactant/cosurfactant until the interfacial tension returns to a +ve value. This process is named "spontaneous emulsification." The addition of co-surfactants into SNEDDS isn't obligatory for many non-ionic surfactants.[33] In SNEDDS Co-surfactants with HLB values ranging from 10 to 14 are employed in SNEDDS. Alcohols with

mediumchain lengths, such as hexanol, pentanol, and octanol, are hydrophilic co-surfactants that minimize the interface between oil and water, facilitating for impulsive microemulsion formation.[34]

Table 2: Commonly used oils, surfactants, and co-solvents.[35,36,37]

General Class	Example	Commercial Name
Medium-chain	Triglycerides of capric/caprylic acids	Captex® 300, 350, Labrafac® CC, Crodamol GTCC
	Di-glycerides of capric/caprylic acids	Capmul® MCM, Akoline® MCM
	Monoglycerides of capric/caprylic acids	Capryol® 90, Capryol® PGMC, Imwitor® 742
Long-chain	Glyceryl monooleate	Peceol®, Capmul®-GMO
	Glyceryl monolinoleate	Maisine®-35
Propylene glycol fatty acid esters	Propylene glycol monocaprylate	Capmul® PG-8, Sefsol 218
	Propylene glycol dicaprylate/caprate	Miglyol® 840, Captex® 200
	Propylene glycol Monolaurate	Lauroglycol® 90, Capmul® PG-12, Lauroglycol® FCC
Polysorbates	Polysorbate esters	Tween® 20, Tween® 80
Castor oil esters	Ethoxylated castor oil	Cremophor®-EL, Etocas® 35 HV
	Hydrogenated castor oil	Cremophor® RH40, 60, Croduret® 40
Polyglycolyzed glycerides	Linoleoyl/Oleoyl Macrogol glycerides	Labrafil® 1944, 2121 CS
	Caprylocaproyl macrogol glycerides	Labrasol®
Polyethylene glycols	Polyethylene glycols	PEG 400, 600
Esters	Glycerol esters	Transcutol®

Mechanism of Self-Emulsification

According to Reiss' theory, emulsification occurs when the entropy changes that favours dispersion is greater than the energy required to increase the surface of dispersion, so the free energy(ΔG) of a conventional emulsion is a (negative) direct function of the energy required to create a new surface between the two phases (oil and water phase) and the emulsion was stabilized. The free energy of a traditional emulsion is related to ΔG and can be represented using the equation below.[8,34]

$$\Delta G = \sum i \; Ni \; r^2 i \; \sigma$$

Where;

G stands for the process's free energy.

N is the total number of droplets.

r is the radius of the droplets.

σ is the Interfacial energy.

The two phases of an emulsion tend to separate over time, reducing the interfacial area. The emulsion is then stabilized by an emulsifying agent, which forms a monolayer of emulsion droplets, reducing interfacial energy and serves as a barrier to prevent coalescence.[38]

PREPARATION OF SNEDDS

The Self-Nanoemulsifying drug delivery system (SNEDDS) is Prepared by two ways.[8]

Preparation of Liquid SNEDDS

It's important method for preparation of self-Nanoemulsifying drug delivery system having the surfactant/co-surfactant ratio and oil/ surfactant/co-surfactant ratio was selected From the Pseudoternary phase diagram. Different concentrations of oil, surfactant, and Cosurfactant were used to process a number of series of the formulation. The oil and surfactant were weighed in appropriate proportions, and the drug was dissolved in this mixture, which was then stored at room temperature.[39]

Preparation of Solid SNEDDS

It is the second most vital method for preparation of Self Nanoemulsifying drug delivery system (SNEDDS). Drug was added into accurately weighed amount of oil in a screw capped vials and melted in water bath if necessary. Then by using a positive displacement pipette the surfactant and cosurfactant were added to the oily mixture and stirred with a vortex to obtain homogeneous solution. Solid Self nanoemulsifying drug delivery system (SSNEDDS) was prepared by adding selected liquid SNEDDS dropwise onto suitable novel adsorbents like Neusillin and are mixed well with glass rod. The damp substance that resulted was sieved no. 120 and dried at room temperature.[39]

METHODS FOR PREPARATION SNEDDS[8]

High energy approach

The formation of a nano emulsion when using high energy approach is based on the mixture composition, which includes surfactant, co-surfactant, cosolvents, and another functional

chemical, and energy is used to prepare the mixture. The emulsion is mechanically processed to become a nanoemulsion.[39]

High Pressure Homogenizer

One of the most significant devices for detecting and preparing nano emulsions is the high-pressure homogenizer. Under very high-pressure conditions the oil in water surfactant mixture under very high pressure and therefore the mixture was pumped by resistive valve. The very high shear stress is liable for the formation of very fine emulsion droplets. The droplet size reduction during homogenization is explained by a combination of two theories: turbulence and cavitation. The high velocity of the resultant mixture gives the liquid a lot of energy, which causes severe turbulent eddies the same size as the mean diameter droplet (MDD) within the homogenizer valve. Droplets were aside from Eddie currents resulting in a reduction in droplet size. At the same time, the pressure across the valve drops, cavitation occurs, and more eddies and disruption droplets form. By reducing the gap size, the pressure of the droplet is increased, leading to a higher degree of cavitation. Emulsion droplets with diameters as small as 100 nm are commonly generated using this method whether there is enough surfactant present to completely cover the oil-water interface formed and thus the adsorption kinetics were high enough to prevent droplet coalescence.[40]

Micro fluidization

It's a crucial tool for identifying and preparing Nanoemulsion. A device known as a "Micro Fluidizer" is used in Micro fluidization technology. This type of device is used in a high-pressure positive displacement pump (500- 300 PSI) that forces the product through the interaction chamber. Micro channels are small channels droplets that are used in high-pressure positive displacement pumps. The product was driven through micro channels and impinged on the impingement area, resulting in very small submicron particles. In the inline homogenizer, two solutions having a mixture of aqueous and oil phase systems are combined and produced, yielding a course emulsion. The coarse emulsion is processed in a micro fluidizer and then further processed to produce a homogeneous, transparent, and stable nano emulsion.[41]

Sonication Method

This method is crucial for determining the size of a droplet and for reducing the size of a droplet in a conventional emulsion using a sonication mechanism. It can only be used on tiny batches of Nanoemulsion.[41]

Phase inversion Method

This type of method is important for preparation of micro emulsion and Nanoemulsion. The tactic is especially based on the response to temperature. Many physical changes occur during this approach, including physicochemical changes, particle size, and in vivo - in vitro drug release rate. Adjusting the spontaneous emulsion formation is used in these strategies. The non-ionic surfactant is often achieved by changing the temperature of the system. The forcing a transition from o/w nano emulsion was formed at low temperature and w/o Nanoemulsion was formed at higher temperature.[42]

Pseudoternary Phase Diagram

Pseudoternary phase diagram is important for determination of SNEDDS. It's diagrammatic representation of oil, surfactant and co-surfactant (Smix), water is known as Pseudoternary phase diagram. It was constructed using the Phase titration and Phase inversion methods. Preparing solutions was step in the process. These solutions, which contained oil and hence had variable surfactant-to-co-surfactant weight ratios, such as 1:1, 2: 1, 3:1, and so on, were vortexed for five minutes, producing in an isotropic mixture. They're being examined to see if they're turbid or clear. The appearance of turbidity in the samples indicates the formation of a coarse emulsion, whereas the appearance of a clear or transparent isotropic solution indicates the formation of a Nanoemulsion (SNEDDS) Percentage of oil, Smix and water. Pseudo ternary phase diagram was created using the values. This diagram corner can illustrate a 100% concentration of each phase's material. The diagram is helpful for presenting information on binary mixtures of two components, such as surfactant/cosurfactant, water/drug, or oil/drug.[43]

Characterization of the SNEDDS[8,5,44,36,97-52]

Droplet size and polydispersity index

The droplet size (z-ave) and polydispersity index (PI value) can be determined by using a photon correlation spectroscopy technique. The sample should be dispersed in a suitable solvent to an appropriate concentration, and mixing would be required in the preparation of the sample.

Zeta potential

The particle charge of formed nanoemulsions can be determined according to the Smoluchowski theory. Zeta potential indicates the stability of the colloidal dispersion. The

formulation would remain stable if it has a high zeta potential, especially when the zeta potential value is more than ± 30 mV.

Morphology

The morphology of the nanoemulsion droplets can be determined by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). The TEM technique would provide the information on the inner structure of the vesicles whereas the SEM technique would provide the surface morphology of the vesicles. The sample might be diluted to a suitable concentration before the measurement.

Self-nanoemulsification time

The efficiency of self-nanoemulsification is assessed using a dissolution apparatus. In general, 1 mL of the SNEDDS is dissolved in 250 mL of water at 37±0.5°C. Gentle agitation is applied by paddle rotating at 50 rpm. SNEDDS are assessed visually according to the rate of emulsification and the final appearance of the emulsion. The time taken for the emulsification is noted. On completion of the emulsification, the samples are taken for particle sizing by photon correlation spectroscopy and further processing by other characterizations.

Percentage transmittance

The percentage transmittance of the system is determined following the dilution of the formulation at 660 nm wavelength by a UVspectrophotometer and using the water as blank. If the percentage transmittance value is closer to 100%, the formulation would indicate a clear and transparent nature.

Viscosity

The viscosity of liquid SNEDDS is generally determined by a viscometer; such as, Brookfield cone and plate viscometer. The viscosity is presented in terms of centipoises, which is related to the shear rate.

Centrifugation study

The formulations were centrifuged using laboratory centrifuge at 5000 rpm for 30 min. The resultant formulations were then checked for any instability problem, such as phase separation, creaming or cracking. Formulation which is stable selected for further studies.[47]

Stability study

The Stability study is important to determine the quality as well as purity of Nanoemulsion system. Stability is determine the tolerance of formulation. The different nanoemulsion formulations was determine for its stability by subjecting them at mechanical stress conditions (centrifugation at 2000- 4000 rpm) as well as formulation was stored at different temperatures ranging from 4 ± 1 °C to 40 ± 1°C for different time intervals. The effect of the mechanical stress conditions on the Physiochemical stability of the nanoemulsion was observed by determining the percent phase separation, breaking of nanoemulsion or any physical change. The studies having no relevant change in the formulations after 60 min of centrifugation at 2000 rpm.[48]

Drug Content

It is important for determination of percent content of drug product as well as percent purity of nanoemulsion system. In this evaluation twenty tablets were weighed individually and the average weigh was noted. Then, all twenty tablets were being crushed together. After that, the average weigh of the sample was taken and diluted, then further analysed using HPLC as in dissolution test and determine percent drug content present in nanoemulsion system.[49]

pH Measurements

The of pH Nanoemulsion formulations was measured by a pH meter or Potentiometer. Electrodes were completely dipped into the semisolid or liquid formulations and pH was noted.[50]

Dispersibility Test

A standard USP XXII dissolution apparatus 2 is used to evaluate the efficiency of self-emulsification of oral nano or microemulsions. At 37 0.5 0C, one milliliter of each formulation was added to 500 mL of water. Gentle agitation was provided by a conventional stainless steel dissolution paddle rotating at 50 rpm. The following grading system has been used to visually assess the formulation's in vitro performance.[51,52]

Table 3: Visual Grading System.

Grade	Time for Emulsification	Observation	Visual Appearance
Grade A	Within 30 seconds	Rapidly forming nanoemulsion which is clear and transparent, high spreadability	Bluish tinge
Grade B	Within 1 min	Rapid nanoemulsion formation which is slightly less transparent, less clear	Bluish white tinge
Grade C	Within 2 min	Rapid nanoemulsion formation, which is turbid in nature formed.	Milky white tinge
Grade D	Within or longer than 3 min	Nanoemulsion devoid of or slow to minimal emulsification, with non uniform distribution of oil droplets	Dull, grayish white tinge having slightly oily appearance
Grade E	Longer than 3 min	Formulation exhibiting either less, poor or minimal emulsification	Large oil globules

APPLICATION[5]

Improving water solubility of poorly water-soluble drug

The Self Nanoemulsifying Drug Delivery System (SNEDDS) is important to improved water solubility of poorly water-soluble drug and increases oral bioavailability of poorly water soluble drug.[54]

Applications of nanoemulsion in drug delivery

Nanoemulsion (SNEDDS) have been applied in various aspects of drug delivery including Cosmetics and transdermal delivery of drug delivery system, cancer therapy, vaccine delivery, Cell culture technology, formulations is important to increases oral delivery of poorly soluble drug, ocular as well as otic drug delivery system, intranasal drug delivery, parenteral drug delivery and pulmonary delivery of drugs as well as intranasal drug delivery system.[55]

Protection against biodegradation

SNEDDS, SMEDDS and SEDDS is important ability to deliver macromolecules like peptides, hormones, enzyme substrates are inhibitors and it is important to protect from enzymatic degradation.

Advancements in Snedds[13]

Supersaturated SNEDDS (s-SNEDDS)

The extent of drug solubility in excipients used for SNEDDS formulation determines the dosage of drug loading. The solubilizing ability of SNEDDS is reduced due to a reduction in lipid content that leads to drug precipitation. Drugs that are highly soluble in surfactants or co-surfactant than lipophilic phase precipitate easily as the solvent ability of these excipients

reduces with dilution. Hence, the majority of SNEDDs formulations contain drugs lower than equilibrium solubility. In one, the presence of large amounts of hydrophilic surfactants also facilitates drug precipitation. To overcome this drawback, s-SNEDDS comprising hydrophilic precipitation inhibitors were studied.[56,57] These s-SNEDDS reduce precipitation of drugs in the GI tract by attaining a metastable saturated state. This mechanism involves the assimilation of polymeric precipitation inhibitors (PPIs) that are water-soluble, resulting in prolonged precipitation time in comparison to mean absorption time. Polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), sodium carboxymethyl cellulose (NaCMC), and methylcellulose (MC) polymers are some commonly used PPIs. Few drugs precipitate in an amorphous state and demonstrate prominently fast dissolution post precipitation when evaluated in vitro. This indicates that the precipitation of such drugs enhances the bioavailability. Few s-SNEDDS were prepared without the use of PPIs by subjecting the formulations to an alternate "heating and cooling cycle."[58,59] s-SNEDDS enhance the stability, concentration vs. time profile, drug release rate, the scope of absorption, drug bioavailability, half-life, and feat of hydrophobic and less lipophilic drugs.[60,61] Recently s-SNEDDS for simvastatin ezetimibe, silybin halofantrine, trans-resveratrol, hydrocortisone, and paclitaxel, were reported to exhibit comparatively higher bioavailability.

Solid SNEDDS

Conservative liquid SNEDDS (L-SNEDDS) are allied with few limitations, like liquid drug-drug interaction, drug-excipients interaction drug precipitation at low temperature, higher cost, delectableness, complex manufacturing, and handling concerns. These limitations are overcome by the solidification of L-SNEDDS. Solid SNEDDS possess enhanced solubility, bioavailability, easier manufacturing procedures, low cost, highly reproducible, higher stability, and scalability.[62] Solid SNEDDS are prepared by adsorption of L-SNEDDS on solid carriers, like aerosil, aeroperl, neusilin, coffee husk, and avicel, using various solidification techniques.[63]

Controlled-Release Solid SNEDDS

SNEDDS pharmacokinetics properties are similar to established oral formulations. They generate rapid absorption resulting in higher Cmax, lower Tmax[64] that causes more fluctuations in plasma drug concentration, which need to be closely monitored. Hence, this increases the need for the development of SNEDDS that possess sustained and controlled release properties without conciliation on bioavailability.[65] The sustained release SNEDDS

have higher bioavailability, lower Cmax, extended mean residence time (MRT) and Tmax, and a notable decline in plasma drug instability. The controlled release of the drug was attained when reconstituted nano-size emulsions were released at zero-order kinetics from the surface orifice of the tablet. The polymers used for controlled release SNEDDS formulations, include HPMC, MCC, poly PLGA, and hydrophobic gelucire.[66]

Mucus Permeation SNEDDS

The mucosal surfaces are roofed with an adhesive mucus layer that enhances the barrier capacity of the mucosa. These mucous barriers are found in the nasal, ocular cavities, lungs, intestines, and vagina. Formulation of mucus gel permeating formulations is a challenging concern.[67] SNEDDS are considered superior mucus permeating nanocarrier. The nanocarriers are believed to cross the mucus layer due to their hydrophobic nature without getting trapped on the layers. The particle size < 50 nm is most favorable for mucous penetration, as the permeability of any formulation is dependent on size.[68] The study showed that SNEDDS with particle size less than 12 nm showed maximum permeation of 70% than 450 nm with a permeation of 8%. The study also showed that modification of charged surfaces would also enhance penetration.[69] The mucoadhesive polymers used in such formulations include HPMC cremophor RH 40 and triacetin.

Bioactive SNEDDS

Bio macromolecules, like lipid, protein, and polysaccharide are considered as modern therapeutic agents due to higher specificity and lower toxicity effects.[70] Pharmaceutical research is evolving with various delivery systems for protein, gene delivery, and other biotechnology products. The larger size and low penetrating ability of biomolecules reduce their bioavailability, hence, is a challenge for incorporating them into formulations, which can be overcome by SNEDDS that are proved to enhance solubility, penetration, and bioavailability of molecules incorporated into it. Sakloetsakun et al. applied insulin/chitosan-TGA SNEDDS formulations for oral drug delivery. They formulated miglyol, cremophor EL, and thiolated chitosan based SNEDDS for the administration of insulin orally. The formulation displayed an increase in drug release compared to the marketed formulation. The in vivo study also shows an increase in serum insulin than other oral insulin solution.[71] Karamanidou et al. formulated mucus permeating SNEDDS for oral delivery of insulin. The developed formulations have enhanced mucus permeability that was affected by ionic strength. The incorporation of Insulin/Dimyristoyl phosphatidylglycerol (INS/ DMPG) in

SNEDDS prohibited an early burst release of insulin, hence, considered a promising way for the oral delivery of insulin.[72]

Self-Double Nano Emulsifying Drug Delivery Systems (SDEDDS)

Proteins and the majority of anti-cancer agents cannot be administrated orally as SNEDDS. Studies recommend that SDEDDS that comprises oil-water-oil emulsions are used for the delivery of peptide and protein drugs.[73] SDEDDS are hydrophilic surfactants containing w/o emulsions that produce w/o/w emulsion on dilution with water followed by gentle agitation. SDEDDS preserve peptides and drugs from enzymatic inactivation in gastro intestinal track (GIT), with improved competence and diminished doses.

Targeted SNEDDS

Improved therapeutic efficacy and reduced toxicity can be achieved by targeted drug delivery. Nanoemulsions remain inside the body for long intervals evading mononuclear phagocytes. Cationic droplets were directed towards an anionic membrane barrier. These formulations are taken up by the liver, thus, aiding targeted delivery. PEGylation is a mechanism, in which polyethelyne glycol (PEG) is connected to a nanodroplet that forms a barrier at the surface, where enzymatic degradation is initiated, thus, increasing stability.[74] HPMC and thiolated chitosan can also be used for the retention of drugs in the GI tract.[75]

Potential of Snedds[13]

The bioavailability enhancement ability of SNEDDS is explained by various in vivo and in vitro methods (Fig. 2). The key discoveries that portray the potentials of SNEDDS are given below.

Enhancing Oral Delivery of Proteins

Peptides have high hydrophilicity, poor permeability, and less stability in the GI tract, thus, making them inefficient for oral delivery. SNEDDS prove to be a better strategy for improving the absorption of proteins. The ion-pair suitablefor protein are used in formulations to enhance protein lipophilicity and decrease leakage. The protein is also conjugated to phospholipids or lipids to avoid leakage of protein from the formulation.[75-77]

Improved Oral Delivery of Natural Phytochemicals

Natural phytochemicals that proved to be potential against cancer, arthritis, hepatitis, and suffer from lower water solubility and low metabolic stability. SNEDDS proved to be an

alternative method for such phytochemicals for enhanced bioavailability, the therapeutic efficacy of various phytochemicals, including triterpenoids, alkaloids, carotenoids, and hepatoprotective agents.[78]

Protection against Biodegradation

The capability of SNEDDS to diminish drug degradation and enhance drug absorption is advantageous for drugs with low bioavailability. The majority of drugs undergo degradation in the body due to acidity of the stomach, enzymatic degradation, and hydrolytic degradation. These drugs can be protected by incorporating them into SNEDDS, which act as a barrier amongst the degrading environment and drug. Drugs, like aspirin, undergo hydrolysis to salicylic acid in the GI tract, thus, degrading. Formulation of this drug into SNEDDS displayed an enhanced plasma profile than normal formulations. The oral bioavailability drug reached 73% that is much higher than normal formulation.[79]

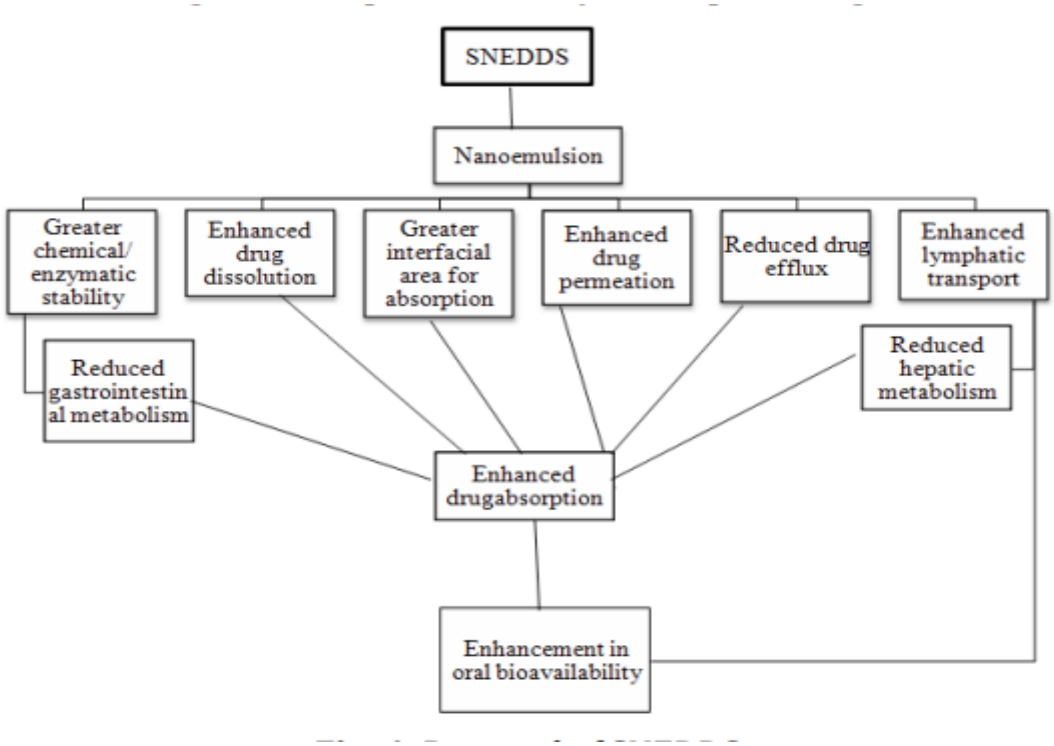

Figure.2

Supersaturable SNEDDS

The supersaturable SNEDDS are formulated with low amounts of surfactant and polymer for prevention of precipitation by the generation of supersaturated state in vivo. This increases drug solubility and guards the drug against deprivation by cholinesterase in that it is highly

adopted for cefpodoxime proxetil (CFP), which posses pH-dependent solubility and the formulation could produce 100% drug release that is independent of pH.[80]

Snedds applied for Enhancement of Bioavailability of Anti-Hypertensive Drugs

Hypertension, defined as an increase in blood pressure approximately affects 1.13 billion people around the world making it one of the most serious medical conditions. The majority of these drugs possess lower bioavailability, shorter half-life, lower permeability, and undesirable side effects. The effective drug delivery system must include lower dosing frequency, higher bioavailability, more selectivity, and reduced side effects.[80] Traditional oral drug delivery techniques reduce the dosage frequency of antihypertensive drugs, which were previously administered twice or thrice a day. The utilization of chemical-dispensing systems, various technologies, like a polymer-coated bead, transdermal therapeutic systems, osmotic pumps and coat-cores, sodium alginate and spheroidal oral delivery absorption systems, and Geomatrix were applied for these agents with the primary goal of reducing lower blood pressure by continuous drug supply all day long. These sustainedrelease systems suffer from delay the time of achieving the pharmacodynamic effect, posses impulsive bioavailability, suffer first-pass metabolism, experience dosage dumping, persistent toxicity, dose obstinacy, and higher costs. Nanotechnology is a potential delivery system for sparingly soluble antihypertensive agents by enhancing their solubility and bioavailability. These also lead to the progress of novel hydrophobic entities. The biocompatibility, colloidal size, drug targeting, lowered dose size, reduced toxicity, and patient compliance are some important advantages of nanosystems. SNEDDS provide larger interfacial areas for drug partitioning and bioavailability enhancement, which donors need for higher-energy emulsification, in turn, reducing manufacturing cost.[81]

Table 4: Marketed formulations of SNEDDS.

Drug	Category	Brand Name	Manufacture	Reference
Telmisartan	Anti-Hypertensive	Micardis	Boehringer Ingelheim	[82]
Valsartan	Anti-Hypertensive	Diovan	Novartis	[83]
Ramipril	Anti-Hypertensive	Altace	Pfizzer	[84]
Lercanidipine HCl	Anti-Hypertensive	Lerez	Glenmark	[85]
Valproic acid	Anti-epileptic	Convulex	Pharmacia	[86]
Cyclosporin A/III	Immunosuppressant	Gengraf	Abbott	[86]
Calcitriol	Calcium regulator	Rocaltrol	Roche	[87]
Ritonavir	Antiviral (HIV)	Norvir	Abbott	[88]

Future Perspective

The advancements in SNEDDS research in the recent past was explored intensively for enhancement of solubility and oral bioavailability of class II drugs. The formulation of liquid SNEDDS to a solid SNEDDS helped to reduce the drug degradation rate but could not eradicate it completely. Therefore, it is vital to recognize micro environment modulation techniques for enhancing the stability of pH-sensitive drugs. The pH catalyzed and solution-state degradation of drugs in SNEDDS is to be studied. Significant research is being conducted for the conversion of liquid SNEDDS to a solid form including tablets and pellets. There exists a necessity to identify an appropriate porous amphiphilic carrier for converting liquid SNEDDS into a solid powder without a major rise in volume and density. The commercialization of SNEDDS depends on the capacity of drug delivery scientists to attend to this aspect of SNEDDS.

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