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A Review of Self-Nano Emulsifying Drug Delivery System

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ABSTRACT

SNEDDS is a well-established technique for increasing the solubility and bioavailability of lipophilic substances. Several formulation strategies are commercially available, owing to the ease of large-scale production and the robustness of SNEDDS. Solidifying liquid SNEDDS improves its stability even further. Patient compliance was higher with controlled release and supersaturated SNEDDS. The availability of biodegradable components and "drug-targeting opportunities" help to distinguish SNEDDS from other solubility improvement approaches. Self-emulsifying drug delivery systems (SNEDDS) are a tried-and-true approach for improving the solubility and bioavailability of poorly soluble compounds. SNEDDS is defined as isotropic mixtures of oils, surfactants, and sometimes co-solvents. When SNEDDS formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/nano) so called as in situ emulsification or self-emulsification. These formulations and methods' ability to produce micro-emulsions or fine oil-in-water (o/w) emulsions with moderate stirring and dilution by water phase in the GI tract could be a viable strategy for lipophilic drugs with dissolution rate-limited absorption. This article attempted to offer an overview of SNEDDS, their mechanism, formulation excipients, SNEDDS potentials, as well as recent improvements, benefits, and drawbacks of SNEDDS formulations and future prospects of SNEDDS.

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INTRODUCTION

1.1.INTRODUCTION TO DRUG SOLUBILITY

The drug's dissolution in solvent media is a critical factor in the formation of a homogeneous system capable of achieving the desired pharmacological activity. To facilitate absorption at the desired site of action, the drugs must be in solution form, and low solubility limits drug bioavailability. Drug solubility issues also necessitate higher doses to achieve therapeutic plasma concentrations after administration with 40 to 50% of novel chemical compounds having low solubility, formulation scientists are still working to formulate these drugs in a way that allows for maximum bioavailability.[5,6] The Biopharmaceutics Classification System (BCS) catalogs drugs into four different classes based on solubility and intestinal permeability of the drug according to the intestinal drug absorption data provided by the United States Food and Drug Administration (USFDA)(Fig.1.1). Drugs possessing lower solubility and high permeability were categorized as class II. The rate-limiting step for these drugs is drug dissolution from formulation and its solubility in gastric fluids but not the rate of absorption. Hence, the enhancement of solubility also enhances drug bioavailability.[1]

1.2 SOLUBILITY ENHANCEMENT TECHNIQUE

The solubility enhancement strategy involves two approaches: the first is the development of formulations to accelerate the first-in-human study without providing any functional link to these formulations used in clinical trials that can be commercialized, and the second is the development of formulations. Fig.1.1 presents various solubility enhancement strategies that primarily involve physical, chemical, or administrative drug modification. Scientists use a variety of techniques, such as particle size reduction, crystal engineering, the formation of soluble salts of drugs, drug complexing, conversion of amorphous to crystalline form, supercritical fluid process, use of additives, and so on, to change the physical and chemical properties of the drug. To increase drug solubility, formulation techniques such as lipid nanoparticles, liposomes, and self-emulsifying formulations were used. The method chosen is heavily influenced by the nature of the drug, the absorption site, and the dosage of the drug.[1]

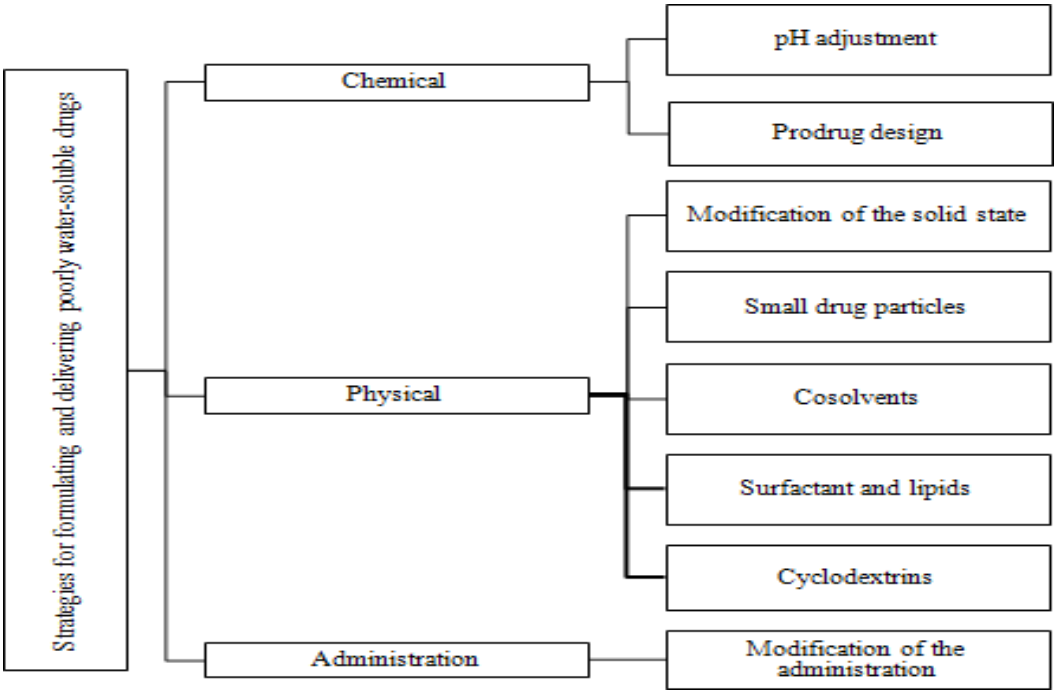


Fig.1.1: Techniques employed for solubility enhancement of drugs.

1.3. INTRODUCTION TO SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM (SNEDDS)

In recent years, promising efforts have been made to exploit the potential of lipid drug delivery systems for enhancing solubility and bioavailability.10 SNEDDS, a lipid-based technique, was shown to increase drug dissolution rate and aid in the formation of soluble drug phases among the various strategies available to date.1 SNEDDS is a competent, well-designed, and patient-acceptable technique for sparingly soluble drugs because it improves solubility, dissolution patterns in the GI tract, permeability, and absorption.8 Because it is similar to solution preparation, the industrial preparation of SNEDDS is less expensive and simpler than that of other Nanocarriers such as liposomes, micelles, polymer-based nanoparticles, carbon nanotubes, or niosomes.[4]

Several factors including its safety, patient compliance, and capacity for self-administration, oral administration remains the best choice for drug delivery. Oral administration has been limited due to the numerous barriers present in the gastro-intestinal (GI) tract, in addition to being the most convenient route of administration.

Drug solubilization within the GI tract is required for drug absorption, as insufficient drug dissolution can result in incomplete absorption, low bioavailability, and high variability after

oral administration. Precipitation, food and drug interactions, susceptibility to degradation, and first-pass metabolism may also be associated with drug oral delivery, resulting in low oral bioavailability.[2]

2. ADVANTAGES OF SNEDDS & DISADVANTAGES OF SNEDDS

2.1 ADVANTAGES OF SNEDDS

➢ By dissolving a large amount in lipids, SNEDDS protects the drug from enzymatic degradation and hydrolysis and makes them suitable carriers for parental transport.

➢ Sensitive drug substance protection.

➢ It has a large O/W interfacial area and extremely low interfacial tension. Low aqueous solubility, low permeability, gastric irritation, enzymatic degradation, and stability are all improved by SNEF.

➢ Drug(s) are selectively targeted toward a specific absorption window in the GI tract.

➢ Increased oral bioavailability allows for dose reduction.

➢ Significant drug load capacities.

➢ It is easily stored because it is a thermodynamically stable system.

➢ Fine oil droplets would pass quickly and promote widespread drug distribution throughout the GIT, reducing the irritation commonly experienced during prolonged contact between bulk drug substances and the gut wall.

➢ As compared with oily solutions they provide a large interfacial area for partitioning of the drug between oil and water.[10-12]

2.2 DISADVANTAGES OF SNEDDS

➢ Due to technological advancements in high-pressure homogenizer and high-coast ultrasonic equipment, SNEDDS formulation has become more expensive in recent years.

➢ Stability is affected by storage conditions such as temperature and pH.

➢ Lack of good predictive in vitro models for evaluating formulations because traditional dissolution methods do not work, and these formulations may be dependent on digestion before drug release.

➢ Different prototype lipid-based formulations must be developed and tested in vivo in an appropriate animal model.[10-12]

3. FACTORS AFFECTING OF SNEDDS

➢ Unless they have extremely good solubility in at least one of the components of SNEDDS, preferably the lipophilic phase, drugs administered at very high doses are not suitable for SNEDDS. The drugs have limited water solubility, and lipids are the most difficult to deliver via SNEDDS.

➢ The ability of SNEDDS to keep the drug solubilized is greatly influenced by the drug's solubility in the oily phase. If the surfactant or co-surfactant plays a larger role in drug solubilization, there is a risk of precipitation because dilution of SNEDDS reduces the solvent capacity of the surfactant or co-surfactant.[14]

4. POTENTIAL OF SNEDDS

Various in vivo and in vitro methods (Fig.4.1) explain SNEDDS's bioavailability enhancement ability. The following are the key discoveries that demonstrate the potential of SNEDDS.[16]

➢ Improving Protein Oral Delivery.

➢ Improved Natural Phytochemical Oral Delivery.

➢ Biodegradability protection.[15]

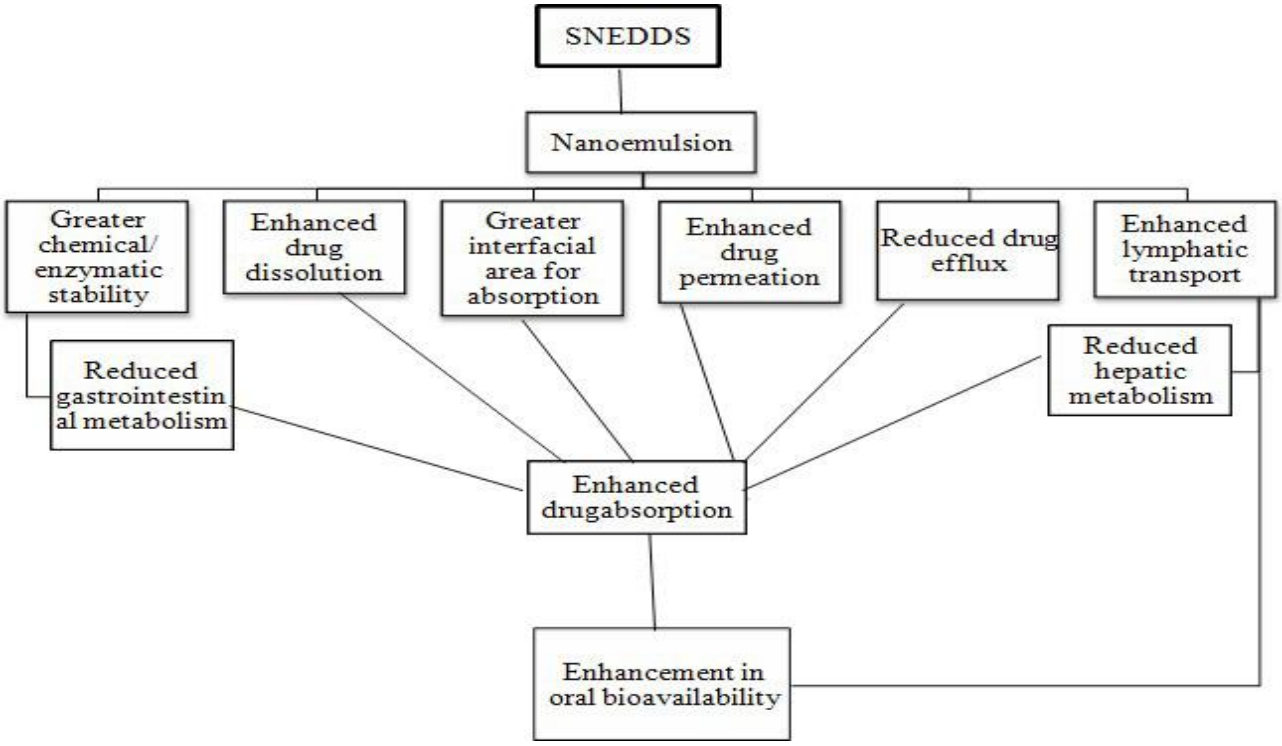


Fig-4.1: -Potential of SNEDDS.

5. MECHANISM OF SNEDDS

➢ After administration, followed by gentle agitation caused by gastric movements, the SNEDDS forms an oil-in-water Nano-emulsion with particles in the Nanometric range (200 nm) immediately and impulsively.

➢ These nanoparticles, which contain the drug that has previously been dissolved in the oil phase, provide a superior interfacial surface for dispersion into GI fluids.

➢ By changing the transport property, the increased interfacial area improves drug solubility and permeability (Fig.5.1). Nano-size droplets digest quickly, allowing for faster drug absorption into the GI tract.

➢ The SNEDDS dosages range from 25 mg to 2 grams.

➢ These are effectively encapsulated as single dosage forms, resulting in improved stability, palatability, and patient acceptance.

➢ They also have a higher drug loading capacity than other lipid-based formulations.[1]

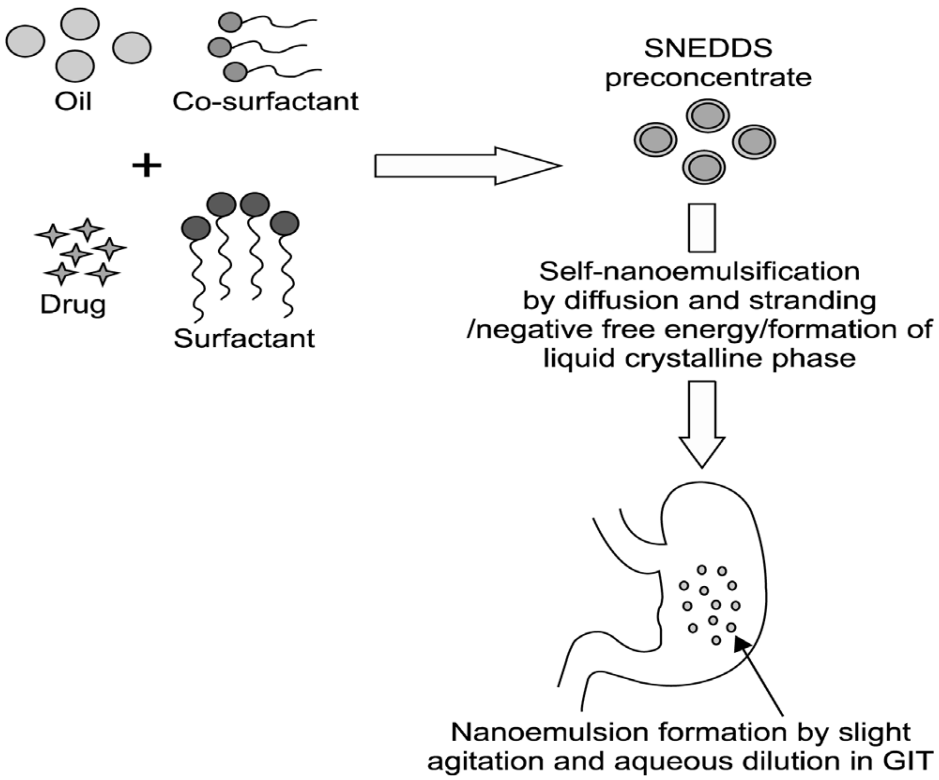


Fig.5.1- Mechanism of SNEDDS.

6. METHODS OF PREPARATION OF SNEDDS

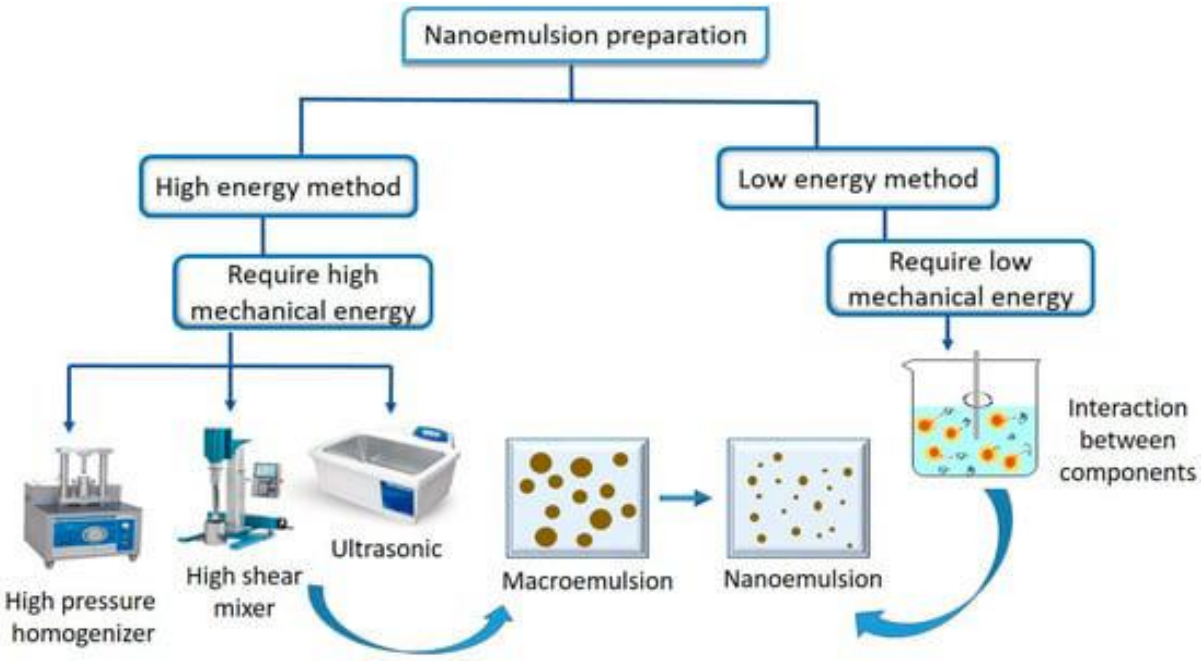


Fig.6.1: - Methods of Preparation.[10]

6.1 COMPONENTS OF SNEDDS

1) Oils

2) Surfactants

3) Co-surfactants

6.1.1) Oils

The oil is used in the formulation of SNEDDS to solubilize the lipophilic drug and ease self-emulsification to increase the amount of drug passing through the intestinal lymphatic system, thereby increasing absorption. Saturation-varying long- and medium-chain triglycerides (LCT and MCT) are used. Because of their inability to solubilize higher drug concentrations, edible oils are not used in the formulation of SNEDDS. Due to the formation of superior, hydrolyzed vegetable oils are used. More surfactant-containing emulsification systems are approved for oral administration. They proposed formulation and physiological compensation. New semi-synthetic medium-chain compounds, known as amphiphilic compounds with surfactant properties, are replacing the oils in SNEDDS.[1, 9]

6.1.2) Surfactants

Non-ionic surfactants with a higher hydrophilic-lipophilic balance (HLB) are morally acceptable. Ethoxylated poly-glycolyzed glycerides and poly-oxyethylene oleate are two commonly used emulsifiers. Natural emulsifiers are thought to be safer than synthetic counterparts, but surfactants have an incomplete self-emulsifying ability. Non-ionic surfactants are less toxic than ionic surfactants and increase permeability through the intestinal lumen.

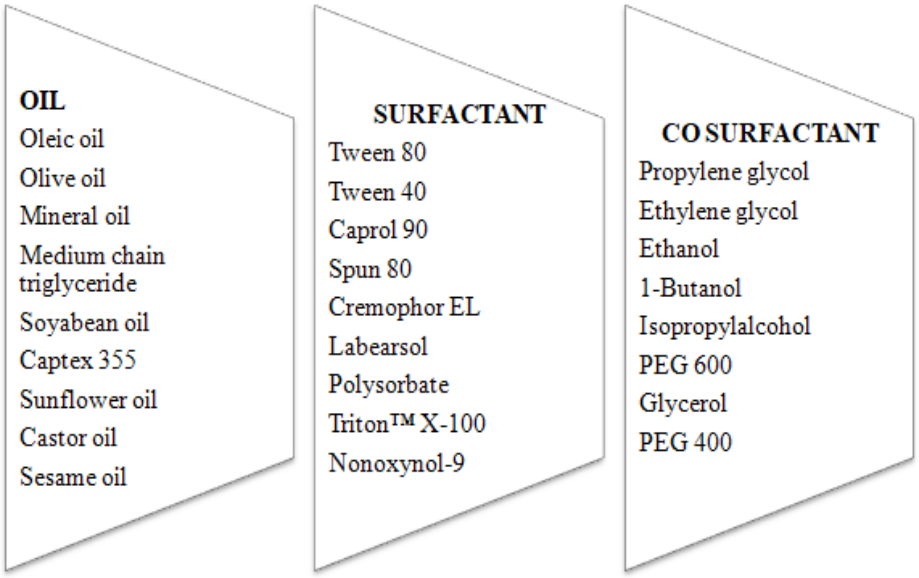
6.1.3) Co-Surfactant

The SNEDDS formulations necessitate relatively higher surfactant concentrations (>30%w/w), which can be condensed by the addition of a co-surfactant. These, together with surfactants, lower the interfacial tension to a negative value, where it expands to form fine droplets, which are then adsorbed with larger amounts of surfactant and surfactant/co-surfactant until the interfacial tension returns to a positive value. This is known as "spontaneous emulsification." Most non-ionic surfactants do not require the addition of co-surfactants to SNEDDS. Co-surfactants with HLB values ranging from 10 to 14 are used in

SNEDDS. Hydrophilic co-surfactants are alcohols with medium-chain lengths, such as hexanol, pentanol, and octanol, which reduce the interface between oil and water, allowing for the formation of impulsive micro-emulsions. (Fig.6.2)[1]

6.2. SELECTION OF APPROPRIATE DRUG CANDIDATES FOR SNEDDS FORMULATION

A formulator's challenges during the formulation of an oral dosage form include solubilizing the drug in the GI tract. SNEDDS increase the rate and breadth of drug absorption. The SNEDDS method is used for BCS class II drugs that have low water.



.**Fig.6.2- List of Oils, Surfactants, and Co-surfactants used in SNEDDS Formulation**

solubility and bioavailability. The administration of these drugs in the form of lipids increases their bioavailability by bypassing the absorptive barrier of reduced water solubility and demonstrating dissolution in the GI by transferring to the bile-salt mixed micellar phase, where absorption occurs readily.[1]

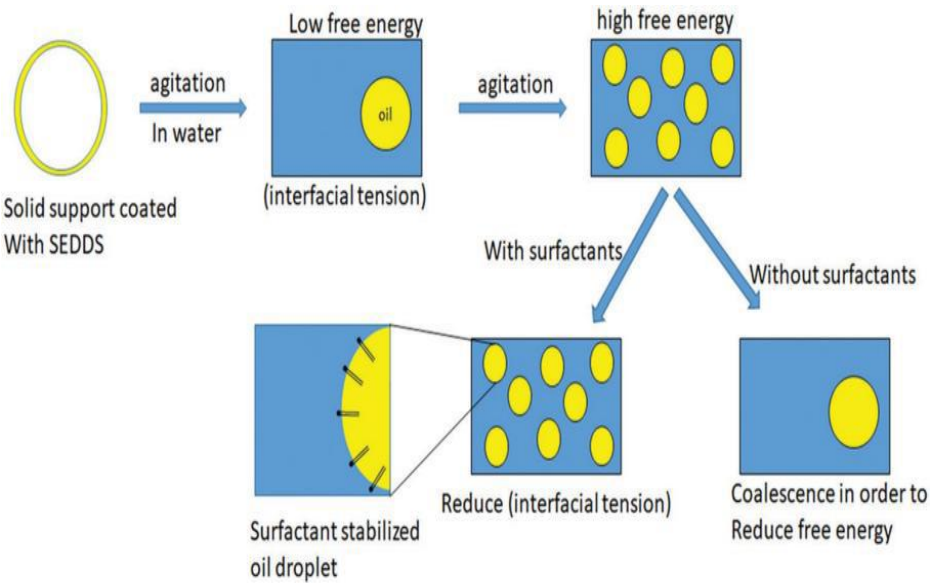


Fig.6.3-: Mechanism of emulsion formation after interaction with aqueous media.

6.3. METHODS USED FOR PREPARATION OF SNEDDS

- Micro-fluidization
- High-pressure homogenizer
- High energy approach
- Sonication method
- Spray drying
- Melt Granulation

6.3.1) MICRO-FLUIDIZATION

A microfluidizer is a device required by the micro-fluidization method. The positive displacement pump forces the product into the interaction chamber. In this system, a microchannel is a small droplet channel. The formed product is then transferred to the impingement area via microchannel, where Nano-emulsion of extremely fine droplets is produced. When the mixture of aqueous and oil phases is added to the homogenizer, course

emulsion is produced. Following further processing, a transparent and uniformly stable Nano-emulsion is formed.[17]

6.3.2) HIGH-PRESSURE HOMOGENIZER

The preparation of Nano-formulation necessitates the use of high pressure. The application of high sheer stress results in the formation of fine emulsion. Turbulence and cavitation are two theories that can explain the droplet size. This method can create Nano-emulsions with droplet sizes smaller than 100 nm. Several factors, including homogenizer type, sample composition, and homogenizer operating conditions such as time, intensity, and temperature, are responsible for the production of Nano-emulsion droplet size using high-pressure homogenizers. High-pressure homogenization is frequently used to create Nano-emulsions of food, pharmaceutical, and biotechnological ingredients.

6.3.3) HIGH ENERGY APPROACH

High mechanical energy is required for the high energy approach which leads the formation of Nano-emulsion by mixing surfactants, oil, and co-solvent. Formulation of Nano-emulsion extensively uses high energy methods. Strong disruptive forces are provided by the high mechanical energy that are used for breaking up the droplets of large size into droplets of Nano size so that Nano-emulsions produced would be of high kinetic energy. SNEDDS require low energy and depend upon the phenomenon of self-emulsification.

6.3.4) SONICATION METHOD

The sonication method is one of the useful methods for the formation of SNEDDS. Ultra-sonication is superior to other high-energy cleaning and operation methods in terms of cleaning and operation. The cavitation forces provided by ultrasonic waves break down macro emulsions into Nano-emulsions in ultrasonic emulsifications. This process reduces the emulsion's droplet size, resulting in a Nano-sized emulsion. The sonication mechanism is responsible for the droplet size reduction.[4]

6.3.5) SPRAY DRYING

Spray drying is a straightforward one-step method for creating solid micro/nanoparticles, including solid SNEDDSs. A solvent is used to mix the solid carrier with the liquid component, which is then solubilized. The solubilized liquid formulation is then sprayed into a hot-air compartment to remove the volatile solvents, which in the case of Nano-emulsion

can be organic solvents or water. Dried particles are prepared at a controlled temperature and flow rate. These micro/nanoparticles can then be filled into capsules or made into tablets.

6.3.6) MELT GRANULATION

Melt granulation is a technique that produces powder agglomeration by adding a softening or binder at a low temperature (50-80^{0}C). Under certain conditions, the melted binder forms liquid bridges between particles and forms small granules that are transformed into spheroid pellets. Depending on the fineness of the powder, 15-25% of the binder can be used. Melt granulation has several advantages over conventional wet granulation because it is a simple operation that eliminates the addition of the liquid component and subsequent drying phases.[2]

7. PHYSICOCHEMICAL CHARACTERIZATION OF SNEDDSs FORMULATION

It is always necessary to calculate the final SNEDDS for each parameter. The general techniques and methods used for SNEDDS characterization are summarized below.

- Visual Evaluation
- Analysis of Droplet size/Particle size
- Morphology
- Zeta Potential Measurement
- Emulsification time measurements
- Viscosity measurements
- Liquefaction time
- Cloud point determination
- Determination of self-emulsification time
- Thermodynamic stability studies
- Turbidimetric test
- Nuclear magnetic resonance (NMR) studies

7.1) Visual Evaluation

Visual inspection aids in determining self-emulsification. After water dilution of SEDDS, the presence of a clear, isotropic, transparent solution suggests microemulsion formation, whereas an opaque, milky white appearance indicates macro emulsion evolution. The absence of precipitation or phase separation indicates that the formulation is stable.

7.2) Analysis of droplet size/Particle size

The type and concentration of the surfactant determine the size of the droplet. The microemulsion formed during SMEDDS dilution with water has a very narrow droplet size distribution, which is essential for optimal drug release, in vivo absorption, and stability. DLS methods are used to analyze droplet size.

7.3) Morphology

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM) can be used to analyze the morphology of the Nano-emulsion droplets. The droplet morphology is determined by back-scattered electrons, which are the basis of SEM. In a transmission electron microscope, electrons are moved through a dispersion to produce the droplet morphology and distinguish between various chemical molecules based on their density. Cryo-SEM and cryo-TEM have been developed recently to investigate the true morphological details of nanoparticles.

7.4) Zeta potential Measurement

The colloidal stability can be ascertained from the zeta potential. By determining the droplets' electrophoretic mobility, it is approximated. Particle aggregation is less likely when there is a high zeta potential value (-40 mV) because of the repellent electrostatic forces present. The medication enclosed in SNEDDSs may not be absorbed orally depending on the charge of the nanoparticles. It has been reported that there is a charge-dependent interaction between mucus and cell membrane barriers regarding absorption enhancement. In addition to shielding the GI epithelium from pathogens and xenobiotics, the mucus thin layer serves as a robust barrier against nanoparticles. Because of electrostatic interactions, the mucus gel has a negatively charged substructure composed of sulfonic and sialic acid, which prevents positively charged nanoparticles from diffusing into deeper mucus regions. As a result, negatively charged nanoparticles can permeate the mucus gel more easily than positively

charged nanoparticles. The apical side of the intestinal epithelial cells, on the other hand, has negative charges due to the mucosal solution in the lumen. As a result, positively charged nanoparticles can interact with the negative charges of the intestinal mucosa, increasing cellular uptake of the encapsulated molecule. In light of this, researchers created SEDDSs that can change their zeta potential using a flip-flop mechanism. They created and incorporated a conjugate compound with both an amino and a phosphate group into SEDDSs. Particles had a negative zeta potential during mucus transport and a positive zeta potential after enzymatic degradation of the phosphate ester group, which resulted in high cell association and uptake.

7.5) Emulsification time measurements

The oil/surfactant and oil phase ratios determine how long it takes to emulsify a formulation. This is determined using basket dissolution equipment, which observes the formation of a clear solution under agitation following the addition of a dropwise formulation to a water-filled basket.

7.6) Viscosity measurements

Viscometers are used to measure the viscosity of SNEDDSs. The viscosity of diluted SMEDDS formulations that are microemulsion is measured using a rheometer, a Brookfield viscometer with a cone and a plate with a rotating spindle. In most cases, liquid SNEDDS formulations are filled into capsules. Low-viscosity formulations are prone to leakage, whereas overly viscous SNEDDSs are difficult to fill into capsules due to flow ability issues. A viscosity of 0.1-1.0 Pa at 25^0C indicates that the formulated SNEDDSs can be easily filled into capsules using liquid filling equipment.

7.7) Liquefaction time

This analysis is carried out to determine how long SNEDDS takes to melt in a simulated GI environment without moving. A transparent polyethylene film covers the dosage form, which is threaded to the bulb of a thermometer. The thermometer should then be placed in a round bottom flask with 250 mL of pepsin-free simulated stomach juice and kept at 37^0C. Next; the measure of time that is required for the liquefaction to happen is noted.

7.8) Cloud point determination

A homogeneous solution's cloud point is the temperature at which it loses its transparency. Surfactants normally lose their ability to form micelles above the cloud point. It is determined by gradually increasing the temperature of the formulation and measuring the turbidity spectrophotometrically. The surfactant's cloud point is the temperature at which the percentage transmittance decreases. Formulations should have a cloud point greater than 37.50 to maintain self-nano emulsification.

7.9) Determination of self-emulsification time

We investigated the emulsification efficiency of several formulations of Tween 85/medium chain triglyceride systems using a primitive nephelometer and a rotating paddle to assist emulsification. This enabled the emulsification period to be calculated. After emulsification, samples were analyzed for particle size using photon similarity spectroscopy, and self-emulsified and homogenized systems were compared. Light microscopy was used to investigate the self-emulsification process. The emulsification process was defined precisely as the erosion of a thin cloud of microscopic particles off the surface of large droplets, rather than a steady decrease in droplet scale.

7.10) Thermodynamic stability studies

The thermodynamic stability of dispersion is an indicator of its kinetic stability and is commonly used to study the chemical reactions that occur between its components. Poor dispersion stability can result in precipitation or phase separation, which can affect drug absorption as well as therapeutic efficacy. Centrifugation, heating-cooling, and freeze-thaw cycles are commonly used in these studies. During these experiments, various aspects such as phase separation, turbidity, and particle size are observed. Following that, stable formulations are chosen for further testing.

7.11) Turbidimetric test

Turbidity is a measurable property that can be used to calculate droplet size and self-emulsification time. A turbidity meter is used to measure the turbidity after administering a fixed amount of SNEDDS to a fixed amount of suitable medium while continuously stirring at 50 rpm on a magnetic stirrer at optimal temperature. The rate of turbidity shift, or rate of

emulsification, cannot be measured because the time required for complete emulsification is too short. The turbidimetric analysis is used to monitor droplet growth after emulsification.

7.12) Nuclear magnetic resonance (NMR) studies

These techniques are used to study the dynamics and structure of microemulsions. Self-diffusion assessments using various tracer approaches, most commonly radio labeling, provide information on the mobility and microenvironment of the components. The magnetic gradient on the samples is used in the Fourier transform pulsed-gradient spin-echo (FT-PGSE) methods, which allow for the simultaneous and rapid measurement of several components' self-diffusion coefficients. The self-diffusion coefficient can be calculated using the Stokes-Einstein equation.

$$D=KT/6\pi\eta r$$

Where T is the absolute temperature, η is the viscosity, K is the Boltzmann constant, and r is the radius of droplet.[2, 4]

8. FUTURE PERSPECTIVES

➢ Recent developments in SNEDDS research have been thoroughly investigated to improve the oral bioavailability and solubility of class II medications.

➢ Although it was not entirely eliminated, the drug degradation rate was decreased by the formulation of liquid SNEDDS into solid SNEDDS.

➢ Thus, understanding how to modify the micro-environment is essential for improving the stability of medications that are sensitive to the pH level.

➢ Drug degradation in SNEDDS that is pH catalyzed and solution-state is to be investigated.

➢ A lot of research is being done on turning liquid SNEDDS into tablets and pellets by solidifying them.

➢ Finding a suitable porous amphiphilic carrier is necessary to turn liquid SNEDDS into a solid powder without experiencing a significant increase in volume or density.

➢ Drug delivery scientists' ability to address this aspect of SNEDDS is a prerequisite for its

commercialization.[1]

9. CONCLUSIONS

Several new, poorly water-soluble chemical species were discovered thanks to drug discovery programs. Lipid-based formulations, and specifically SNEDDSs, have significant potential to improve oral absorption, aqueous solubility, and stability, and reduce inter- and intra-patient dose variability. Through several mechanisms, including enhanced membrane fluidity, avoiding the first-pass effect, and inhibiting P-GP efflux, SNEDDSs enhance drug absorption. Previously, oral bioavailability and low aqueous solubility of medications were addressed with SNEDDS formulations. The scope of SNEDDSs, however, goes far beyond the problems with solubility and dissolution. They have now developed into solid, mucus-permeating, supersaturated, targeted, and SNEDDSs, which address problems with traditional SNEDDSs and bring about novel changes for a variety of applications. SNEDDS formulations improved the solubility, stability, and bioavailability of several anti-viral, anti-diabetic, and anti-cancer drugs.

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