Review Article

Self-Nanoemulsifying Drug Delivery System - An Overview

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ABSTRACT

In order to boost the better and desired bio-availability of in vitro drugs and to increase their clinical efficacy when administered orally, the main objective of this present thesis is to develop the current Self Nano-emulsifying drug delivery method. Context: SNEDDS is intended for lipophilic drug intensification [or] poorly aqueous dissolvable products. NE has blends of tar, SURFACTANT, Co-SURFACTANT, and includes cosolvent, as well. The mixture has to be isotropic in nature. It contains a micro (or) nano-emulsion of the drug-containing oil that is spontaneously aqueous to mild agitation media. SNEDDS is the most important application for increasing the solubility of lipophilic drugs in the Biopharmaceutical Classification System [BCS class] II and IV drugs. Using the Continuous-emulsification process, NE fats improvised and enhanced the orally bioavailable quality of a poorly-aqueous dissolvable drug material. SNEDDS is a new approach to drug-delivery-system which are substantially intravenous [parental], optic [or] preparation (optic or ocular) intra-nasal, suppository, oral (sustained release results, pellets forms) and finally cosmetics. Result: SNEDDS greatly demonstrates the increased rate of dissolution and prevents interfacial stress. In aqueous media such as gastrointestinal fluid, SNEDDS under dilution and emulsion types [stable]. The emulsion is water-type oil[o/w] and has a globule of less than 150 Nano-meters in size.

Keywords: Nano-emulsion, Bi-continuous SNEDDS, Pseudo-ternary phase diagram.

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INTRODUCTION

The Self nano emulsifying Drug Delivery System (SNEDDS) is an isotropic blend of natural or synthetic oil, surfactants and co-surfactants with an unusual ability to form fine oil-in-water (O/W) nano-emulsions accompanied by aqueous media under moderate agitation. Under water dispersion, the self-Nano emulsifying drug delivery device with a size range of globules is less than 100 nm. The Self-Nano Emulsifying Drug Delivery System (SNEDDS), the Self-Micro Emulsifying Drug Delivery System (SMEDDS) and the Self-Emulsifying Drug Delivery System (SEDDS) have been used in recent years to increase the aqueous solubility of drugs that are poorly water soluble. For oral ingestion, the formulation of the self-nano-emulsifying Drug Delivery Method was formulated using medium chain tri glyceride oils and non-ionic surfactant. The drug was subjected to the dissolution rate limiting absorption, the drug was substantial under SNEDDS for enhancing rate as well as drug absorption and reproducibility of drug concentration plasma profile. It is critical that the SNEDDS is one of the Stable Nano emulsions to provide a wide interfacial area for drug partitioning between the oil and the aqueous phase. Getting a higher drug dissolution rate and increasing the bioavailability of the formulation of drugs. The thermodynamically stable and transparent or translucent non-ionized dispersion of (o/w) and (w/o) nano emulsion was stabilized by the addition of surfactant and co-surfactant molecules to the Self Nanoemulsifying drug delivery method. Nanoemulsion, mini emulsion, ultrafine emulsion, submicron emulsion are often referred to as the Self Nanoemulsifying Drug Delivery System. Self Nanoemulsifying Drug Delivery System (SNEDDS) o/w nanoemulsion under moderate agitation accompanied by aqueous media to form stable o/w nanoemulsion under aqueous media [1].

Appropriate drug candidate for SNEDDS

Self-nano emulsification formula selection criteria increase oral bioavailability of drugs belonging to biopharmaceutical classifications II and IV, log p value should be greater than 4 and melting point should be minimum, oil droplet size should be less than 100nm, optically transparent when dispersed, HLB value should be greater than 12[2].

Factors affecting SNEDDS

Drugs administered at extremely high doses are not appropriate for SNEDDS unless they are highly soluble in at least one of the SNEDDS components, ideally in the lipophilic step. The drugs show minimal water solubility and SNEDDS is the most difficult to deliver lipids.

SNEDDS' ability to retain the drug in a solubilized state is significantly affected by the solubility of the drug in the oily phase. If the surfactant or co-surfactant contributes to

drug solubilization to a greater degree, then there could be a chance of precipitation, as SNEDDS dilution may lead to a reduction in the solvent potential of the surfactant or co-surfactant [3].

Nanoemulsions classification

Depending on the composition, the nanoemulsions are most likely to be formed.

Water in oil (W/O) Nanoemulsion

In which droplet of water in Continuous Phase oil was dispersed.

Oil in water (O/W) Nanoemulsion

The Oil droplet in Continuous Phase Water was distributed.

Bi-continuous Nanoemulsion

In which surfactant in both the oil and water phase was soluble and droplet was distributed in both the oil and water phase4[4].

Advantages of the Drug Delivery Device Self Nano Emulsifying (SNEDDS)

1) Compared to micro emulsions, nanoemulsions (SNEDDS) have a very wide surface area and free energy (SMEDDS).

2) The Drug Administration's self-emulsification method is critical for improving bioavailability.

3) In addition to their ability to protect drugs from hydrolysis and enzyme degradation, the ability of nano emulsion (SNEDDS) to dissolve large quantities of lipophilic drugs makes them suitable for parenteral transport vehicles.

4) It is necessary for SNEDDS to provide ultra-low interfacial voltage and to provide a wide O/W interface field.

(5) Nanoemulsion (SNEDDS) has been developed in a number of formulations, such as liquids, aerosols, foams, creams, ointments and gels, and is used in the pharmaceutical field as a nanoemulsion, as well as in the drug delivery system for oral, topical and parenteral nutrition.

6) In the Self-Nanoemulsifying Drug Delivery System (SNEDDS), the number of applications in medicine, food, drinks, storage, cosmetics and also in the perfume and pharmaceutical industries are important for oils and their main components.

7) It is used as an Ayurvedic and Unani system.

8) An automatic system of drug administration (SNEDDS) that has a specific and specific system of drug administration.

Dis Advantages of Self Nano Emulsifying Drug Delivery System (SNEDDS)

1) Nanoemulsion preparations (SNEDDS) are difficult to prepare since the high-pressure homogenizer and ultrasonic equipment were available in the past year and the preparation of nanoemulsion was costly.

2) The stability of the delivery system of self-nanoemulsifying drugs was influenced by temperature and pH [5].

Operation/ Method/ Mechanism

Self Nano-emulsification occurrence, Modification in entropy would help the dispersion is higher than the energy needed to increase the dispersion surface, hence the traditional emulsion free energy.

1. Oil phase

SNEDDS are isotropic mixtures of oil, surfactants and co-surfactants which, upon mild agitation, form fine oil-in-water nano emulsions, followed by injection into aqueous media, such as GI fluids. As its properties control the solubility of the drug, the oil step should be chosen appropriately for the drug. This also influences the emulsion droplet size and the rate at which emulsification occurs. For good emulsification to occur, a small droplet size is necessary. After overnight shaking of drugs with specific amounts of various oils with the substance, solubility can be measured by HPLC. Hence, by characterizing several oils, the most appropriate oil can be picked. To achieve the optimal solubility of the medication, mixtures of oils may also be used. [6]

2. Surfactant

The design of self-emulsifying systems may have various compounds exhibiting surfactant properties, but the choice is restricted at the same time as very few surfactants are orally acceptable, because safety is a major deciding factor in the choice of a surfactant. Natural-origin emulsifiers are favoured because they are considered safer than synthetic surfactants. Non-ionic surfactants with a relatively high hydrophilic lipophilic balance are the most extensively suggested (HLB). 30-60% surfactant concentration is used to shape stable SEDDs.

The four big surfactant groups are-

1) Anionic surfactants: Potassium laurate, sodium lauryl sulphate.

2) Cationic surfactant : Quaternary ammonium halide.

3) Ampholytic surfactants: Sulfobetaines.

4) Nonionic surfactants: Sorbitan esters (Spans), poly – sorbates (Tweens) [7].

3. Co-solvent/co-surfactant

The use of single surfactants rarely achieves stable interfacial tension; the addition of co-surfactant is therefore necessary. The addition of co-surfactant leads to

a decrease in interface bending stress and allows ample versatility for the interfacial film to take up the different curvatures needed to form microemulsions/ nanoemulsions. Together with surfactants, HLB co-surfactant 10-14 is used to decrease the oil water interface, fluidize the hydrocarbon region of the interfacial film and allow spontaneous micro-emulsion formation. In addition to shaping microemulsion shape, the option of co-surfactant and surfactant is important for solubilization in microemulsions[8].

4. Consistency builder

To modify the stability of the emulsion Tragacanth, cetyl alcohol, stearic acid or beeswax can be added to formulate SMEDDS/SNEDDS.

5. Polymer

For the formulation of sustained release SMEDDS, an inert polymer matrix representing 5 to 40 % of the composition relative to weight which is not ionizable at physiological pH and capable of forming a matrix is used. Hydroxypropylmethyl cellulose and ethyl cellulose are examples [9].

6. Solid carrier

Solid carriers can be microporous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers, or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium aluminium silicate (Neusilin) microporous calcium silicate (Florite TM RE) magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose, and cross-linked polymethyl methacrylate can be adsorbed at high levels (up to 70%w/w) onto suitable carriers.

METHODOLOGIES

Solubility Studies

The solubility of the drug in different oils, surfactants, co-surfactants and oil was calculated using the shake flask method for the surfactant mixture. In each car, an excess amount of drug was added, followed by vortex mixing for 30 seconds (Remi mixer, Mumbai). Mixtures were shaken in a thermostatically regulated shaking water bath for 48 h at 30°c, followed by equilibrium for 24 hr. Mixtures were then centrifuged for 10 min at 3000 rpm and a Millipore membrane filter (0.45µ) filtered the supernatant. The samples were appropriately diluted with methanol and the concentration of the drug was obtained using the UV-validated procedure [10].

Preliminary Surfactant Screening

Different surfactants were tested for emulsification capacity for oral use. In short, 150 mg of the surfactants were applied to the oily step of 150 mg. The mixtures for homogenization of the components were gently heated at 500C. Every mixture, 100 mg, was then diluted in a stoppered conical flask with distilled water up to 100 ml. The number of flask inversions needed to produce homogeneous emulsion was assessed by the ease of emulsification. Emulsions were permitted to stand for 2 h and the UV-Visible spectrophotometer (Shimadzu, Japan) used distilled water as a blank to determine their percentage transmittance. In addition, emulsions for any turbidity or phase separation were observed visually.

Preliminary screening of co-surfactants

For further screening of the various co-surfactants for their emulsification potential, the chosen oily phase and surfactant were used. Mixtures of co-surfactant 200 mg, cremophor RH40 400 mg, and sunflower oil 600 mg were prepared and evaluated in a manner similar to that defined in the surfactant preliminary screening.

Pseudo ternary phase diagrams

Using the water titration process, pseudo-ternary phase diagrams of oil, surfactant/cosurfactant (S/Co S), and water were created. The oil and S/Co S mixtures were diluted with water in a drop-wise manner at certain weight ratios. A transparent and homogeneous mixture of oil and S/Co S was developed by vortexing for 5 min for each phase diagram at a particular ratio of S/Co S (i.e.,1:1, 2:1 w/w). Then, for phase clarification and flowability, each mixture was titrated with water and visually examined. From the weight measurements, the water concentration at which turbidity-to-transparency and transparency-to-turbidity transformations occurred was obtained. These values were then used to evaluate the microemulsion domain boundaries corresponding to the oils' selected value, as well as the (S/Co S) mixing ratio. In the presence of a drug using drug enriched oil as the hydrophobic portion, phase diagrams were also constructed to determine the effect of drug addition on the microemulsion boundary. Phase diagrams were then constructed using TRI-PLOT V-1.4 software by David Graham (Loughborough University).

Nanoemulsion Preparation Methods

Various methods have been proposed for the preparation of nano emulsions, which can be divided into high-energy (relying on mechanical devices) and low-energy (relying on phase changes) methods.

Methods for High-Energy

Using equipment such as high-pressure homogenizers, microfluidizers and ultrasonic homogenizers, the production of nano emulsions in high-energy methods is carried out. Some of the characteristics of high-energy approaches include greater regulation of the distribution of the size of droplets and the need for a low surfactant concentration. Nevertheless, there are many drawbacks to the method, including low thermodynamic efficiency that contributes to increased use of resources. A further drawback of this approach is the production of a large temperature during the creation of a product. Some of the high-energy strategies are seen as follows:

Sonication

Sonication is the best preparation tool for nano emulsion. The input energy is given by a probe sonicator in this technique, and with the sonication mechanism, the size of emulsion droplets is reduced. However, for the processing of a large number of nano emulsions, this method is not suitable and can only prepare low quantities of nano emulsions [11].

Microfluidizers

We can manufacture emulsions at pressures above 700 MPa with this technique. Two microchannels flow through the initial emulsion solution and collide in a chamber, which eventually leads to a reduced droplet size. Therefore, this process produces an emulsion of small droplet sizes. [11]

Low-energy Methods

In low-energy processes, which involve a phase inversion process and a spontaneous emulsification method, the phase transition from oil to water or water to oil takes place. The need for a precise range of surfactant and oil types, the need for high volumes of synthetic surfactants and limited industrial production potential are some of the constraints of low-energy methods [11].

Phase Inversion Method

In this process, during the emulsification time, the dispersion of droplets is obtained by the chemical energy provided by the phase transfer resulting from a change in composition at a constant temperature or with a constant change in temperature. The temperature of the inversion process is the temperature at which the nano emulsion of the water-in-oil becomes the nano emulsion of the oil-in-water. The solubility of the surfactant is higher in water at lower temperatures and the oil nano emulsion is produced in water. In other words, if a system is unexpectedly diluted with water at a higher temperature than the phase inversion temperature, the temperature is below the phase inversion temperature and a sudden shift in the phase occurs. Therefore, the nano emulsion is changed from the water-in-oil state into the oil-in-water state [11].

Solvent displacement method

From the nanoprecipitation process used for polymeric nanoparticles, the solvent displacement method for spontaneous fabrication of nano emulsion has been adopted. The oily phase is dissolved in water-miscible organic solvents such as acetone, ethanol, and ethyl methyl ketone in this process. The organic phase is poured into a surfactant-containing aqueous phase to yield spontaneous nano emulsion by rapid organic solvent diffusion. The organic solvent is extracted by a suitable means, such as vacuum evaporation, from the Nano emulsion [12].

EVALUATION

Droplet size

In self-emulsification results, droplet size is a deciding factor since it determines the rate and extent of drug release, as well as the emulsion stability. Photon correlation spectroscopy, microscopic techniques or a Coulter Nano sizer are the methods that are primarily used for determining droplet size. Wang et al. found that the rate of ibuprofen release was dependent on the mean droplet size in dilute media of carrier emulsions produced from SNEDDS. More than 95% of the encapsulated ibuprofen was released within 30 minutes by SNEDDS that generated nano emulsion of droplet size 58 nm, which was significantly faster than the control experiment using a traditional tablet [12].

Measurement of Viscosity

A modular compact rheometer (MCR 102, Anton Paar Instruments Ltd, Graz, Australia), fitted with a temperature control system, was used to assess the viscosity of the formulations. For the measurements, a parallel plate was used (50 mm). The gap size was set at 500µm with the use of 4µL of each pre-concentrated SNEDDS. The shear stress was measured at varying rates from 0.1 to 100 s−1 for 5 min. All rheological measurements were made at 25 °C, and data were analysed with Rheo compass software (version 1.13.44-release, Anton Paar Instruments Ltd, Graz, Australia) [13].

Determination of emulsification time

In order to measure the emulsification efficiency of the Tween 85 method with MC triglyceride, Pouton used a spinning paddle to facilitate crude nephelometer emulsification. This allowed for the time taken for emulsification to be calculated. Samples were taken for particle sizing by photon correlation spectroscopy upon completion of emulsification, and self-emulsified systems were contrasted with homogenized systems. Using light microscopy, the self-emulsification mechanism was observed. The mechanism of emulsification was found to involve erosion of a fine cloud of small particles from the surface of large droplets, rather than a progressive reduction in droplet size [14].

Solubility Test for Dye

The type of nano emulsion is verified by a water soluble dye (Eosin) sprinkled on the surface of the prepared formulation and observed for spontaneous dispersion [15)].

Measurement of Conductivity

Conductivity Calculation based on the phenomenon of phase inversion defines the point of addition of the aqueous phase where the oil phase has continuously shifted in the continuous water phase [15].

Measuring Turbidity

Hatch turbidity meter, Orbeco- Helle turbidity meter equipment used for turbidity calculation by equilibrium phase dispersion [15].

Drug - Excipient compatibility studies:

In order to analyse the drug excipient interactions, Fourier transform infrared analysis (SHIMADZU) was performed. Samples were scanned in the 400-4000cm-1 range [16].

Determination of zeta potential

The zeta potential is a tool for calculating particles' surface charge when put in liquid. The potential of Zeta is used to predict the stability of dispersion and its value depends on the physicochemical properties of the drug, polymer, vehicle, electrolyte presence, and its adsorption. It is calculated by the Zetasizer Malvern instrument. Nanoemulsion is diluted for the calculation of zeta potential and its value is estimated from the electrophoretic mobility of oil droplets. It is assumed that a zeta potential of ±30 mV is adequate to ensure nanoemulsion physical stability. By using Malvern Zetasizer for risperidone nanoemulsion, Đor ević et al. obtained zeta potential of around-50 mv [17].

Transmission Electron Microscopy (TEM)

The transmission electron microscopy analysis provides data on the surface morphology of the resulting nano emulsion and size by diluting the water-diluted samples 1000 times and obtaining the formulation size.

Dispersibility tests

A standard USPXXII dissolution apparatus 2 was used to test the efficiency of the dispersibility of the formulation. One ml of each formulation was applied to 500 ml of water at around 37±0.5 C, respectively. Gentle agitation was provided by a regular stainless steel dissolution paddle spinning at 50rpm. Using the grading system as shown below, the in vitro performance of the formulations was visually assessed.

Grade A: Rapidly forming (within 1 m) nanoemulsion, having a clear or bluish appearance. Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance. Grade C: Fine milky emulsion that formed within 2 m.

Grade D: Dull, greyish white emulsion having slightly oily appearance that is slow to emulsify (longer than 2 m).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules [18]

Drug content

Drugs are extracted from pre-weighed SEDDs by dissolving them in the necessary solvent. The drug content in the solvent extract was measured against the normal solvent solution of the drug using a suitable analytical process [19].

***In Vitro* Diffusion study**

In vitro diffusion tests, using a dialysis technique, were performed for all the formulations produced. Phosphate buffer pH 6.8 was the dialysis medium. The thread was connected to one end of the pretreated cellulose dialysis tubing (7 cm in length) and then 1 ml of self-nano-emulsifying formulation and 0.5 ml of dialyzing medium were inserted in it. In addition, the other end of the tube was secured with a thread and permitted to rotate freely in 200 ml of dialyzing medium and continuously stirred at 100 rpm with a magnetic bead on a 37 °C magnetic plate. Aliquots of 1 ml at various time periods were removed and further diluted. Every time, the amount of aliquots was replaced with fresh dialysis medium. These samples were analyzed quantitatively for drug dialyzed across the membrane at corresponding time by using UV-visible spectrophotometer [3].

Fourier-transform infrared spectroscopy (FTIR) spectral analysis

For the assessment of drug excipient interaction, polymerization, crosslinking as well as drug loading in the formulation, FTIR analysis can be performed. It is also used to identify the functional groups with their means of attachment and the molecule's fingerprint. A molecule resides in the ground state at low temperature, and they get excited to higher energy states as they consume the radiant energy. The determination of this energy difference (ΔE) between the excited and ground states of the molecule is based on IR spectroscopy. For performing FTIR, sample can be prepared by employing suitable method such as potassium bromide pellet method, Nujol mulls and then sample is scanned in FTIR at moderate scanning speed between 4000- 400 cm^{-1}. Srilatha *et al.* conducted FTIR studies on pure drug and glipizide nanoemulsion and reported absence of drug excipient interactions (hence compatibility of drug and excipient) as all the characteristics peaks of drug appeared at same point in formulation [20].

APPLICATIONS OF NANOEMULSION

For the development of pharmaceutical preparations, nanoemulsions containing pharmaceutically active agents can be used. A specific galenic type can be imparted to the mixture if desired. Ampoules, especially sterile solutions for injections and infusions; Solutions, in particular oral liquids, eye drops and nose drops, which may contain various auxiliary substances, may be formulated in the form of nanoemulsion; aerosols, which may contain propellant gas and stabilizers in addition to nanoemulsion, without metering features and dosing aerosols; ; hydrophilic and hydrophobic gels and nanoemulsion-containing ointments; nanoemulsion-containing o/w or w/o creams; lotions and nanoemulsion-containing pastes are available on the market.

Ocular delivery

Oil in water emulsions are being explored for improved topical lipophilic drug delivery to the eye. Examples: Piroxicam, Pilocarpine, Indomethacin, cyclosporine A

Percutaneous route

There is low skin permeation in many medications, resulting in poor efficacy. Organic solvents are common chemical skin penetration enhancers that are normally associated with skin irritation, toxicity and sensitization to some degree. A solvent free topical vehicle based on drug entrapment in the o/w emulsion droplets of submicron size is more efficacious in terms of percutaneous absorption with possibly devoid of adverse effects.

Examples: NSAIDs, Diazepam, α-tocopherol antifungal drugs (Econazole or Miconazole nitrate) EMLA (Eutectic Mixtures of local anaesthetic) have proven to be useful medication by this route.

Nasal route:

Due to numerous advantages over parenteral and oral administration, especially by bypassing the liver, the nasal route has received great attention. By solubilizing the substance in the inner process of an emulsion and prolonging the contact time between the emulsion droplets and the nasal mucosa, nanoemulsions improve absorption.

Examples: Lipid soluble renin inhibitor was incorporated into an O/W emulsion, insulin and testosterone can also be delivered by this route.

Use of nanoemulsion in cosmetics

As potential vehicles for the regulated delivery of cosmetics and for the optimized dispersion of active ingredients into the skin, nanoemulsions have recently become more and more relevant. Due to its own bioactive effects, nanoemulsion is gaining growing interest. As there is no inherent creaming, sedimentation, flocculation or coalescence found with macro emulsions, nanoemulsions are appropriate in cosmetics.

Antimicrobial Nanoemulsions

Antimicrobial nanoemulsions in water droplets ranging in size from 200-600n.m are oil. The particles of the nanoemulsion are thermodynamically guided to fuse with species that produce lipids. They release part of the energy stored in the emulsion when enough nano particles fuse with the pathogen.

CONCLUSION

For BCS class II or IV and drug compounds with low aqueous solubility, SNEDDS is a promising approach. The process used for lipophilic drugs offers faster dissolution rates for the resulting emulsification. SNEDDS, which has been shown to greatly boost oral bioavailability with the potential advancement of this technology, will make oral delivery of hydrophobic drugs possible. SNEDDS will continue to allow novel drug delivery applications and solve problems associated with the delivery of drugs that are poorly soluble [20].

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