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Review Article

SELF NANO-EMULSIFYING DRUG DELIVERY SYSTEM: A REVIEW

Mrunal P. Divate, Shravani U. Bawkar, Rita D. Chakole, Manoj S. Charde*

Post Graduate Department of Pharmaceutics, Government College of Pharmacy, Vidyanagar, Karad, Satara, Maharashtra, India

**Corresponding author: manojudps@rediffmail.com*

ABSTRACT

Developments in recent drug discovery programs, yields a large proportion of novel pharmacologically active molecules that are lipophilic and poorly soluble, which is a major challenge for pharmaceutical researchers to enhance the oral bioavailability of such drug molecules. The self-nanoemulsifying drug delivery system (SNEDDS) is a promising Drug Delivery System which is well known for its prospective to improve the aqueous solubility and oral absorption of poorly water soluble drugs. SNEDDS is an isotropic mixture comprising oil, surfactant, co-surfactant and drug that form oil in water emulsion in aqueous environment under placid agitation. It can readily disperse in the aqueous environment of the gastrointestinal tract to form a fine oil-in-water emulsion with a droplet size not exceeding 100 nm under mild agitation for improving the oral bioavailability of poorly water-soluble drugs. The self nano-emulsifying Drug Delivery System (SNEDDS) is applicable on BCS Class II and Class IV Drugs for improving water Solubility of poorly water soluble drugs. It is the novel drug delivery system which is applicable for oral, parenteral, ophthalmic, intranasal and cosmetic delivery of drugs. The review presents an overview of design of formulation, preparation of components, mechanism of self-emulsification, biopharmaceutical aspects and evaluation of self nano-emulsifying drug delivery system (SNEDDS) for enhancement of oral bioavailability of poorly water soluble drugs.

Keywords: Self nano emulsifying drug delivery system, Bioavailability, Solubility, Pseudo ternary phase diagram.

1. INTRODUCTION

As oral route is the most preferred route for administration of drugs, but majority of drugs are frequently administered through oral route because of first pass metabolism. But about 40% of new drug candidates have poor aqueous solubility and the oral delivery of such drugs is complicated because of the reason that of their low bioavailability, high inter/ intra-subject variability, and no dose linearity [1, 2]. Nanotechnology has become a most promising technology in pharmaceutical sciences and it astonishingly influenced drug delivery research over the last two decades and various efforts are ongoing to extend its applications in various streams of pharmaceutical sciences, for example, many nanoscale carriers have been recently explored for improving therapeutic performance of drugs. Different ways through which nanoscale technologies improves the therapeutic efficacy of drugs are:

- Improves solubility of hydrophobic drugs (Class II and IV drugs as per the Biopharmaceutical Classification System [BCS])
- Improves permeability or transport of poorly permeable drugs (class III and IV drugs as per the Biopharmaceutical Classification System [BCS])
- Modulates distribution and drug disposition of drugs
- Prevents degradation of drugs in physiological milieu
- Enables targeted delivery of the drugs to the site of action.

Self nanoemulsifying drug delivery system is one of the promising approaches to overcome the formulation difficulties of various hydrophobic/lipophillic drugs and to improve the oral bioavailability of poorly absorbed drugs [3, 4]. Self-nanoemulsifying Drug Delivery system (SNEDDS) is isotropic mixture of natural or synthetic oil, surfactants and co-surfactants that have a unique ability of forming fine oil-in-water (O/W) nano-emulsions under mild Agitation followed by addition of aqueous media [5].

1.1. Advantages of SNEDDS

i. SNEDDS have much larger surface area and free Energy than micro emulsions (SMEDDS) [6].

ii. The self Nanoemulsifying drug delivery system improves the Bioavailability [7].
iii. The ability of nanoemulsion (SNEDDS) to dissolve large quantities of lipophilic Drug, along with their ability to protect the drugs from hydrolysis and enzymatic degradation make them ideal vehicles for the purpose of parenteral transport [8].
iv. SNEDDS provides ultra-low interfacial tension and providea large o/w interfacial area [9].
v. Potential advantages of these systems include, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut. Thus, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate and extent of absorption and result in more reproducible blood time profiles [10].
vi. Ease of manufacture and scale- up is one of the most important advantages that make SNEDDS unique when compared to other drug delivery systems like solid dispersions, liposome, nanoparticles, etc., as they require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large- scale manufacturing. This explains the interest of pharmaceutical industry in the SNEDDS [10].

1.2. Disadvantages of SNEDDS [10, 11]

i. Drugs which are administered at very high dose are not suitable for SNEDDS.
ii. The drugs exhibiting limited solubility in water and lipids are most difficult to administer as SNEDDS.
iii. The potential of SNEDDS in maintaining the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase.
iv. If the surfactant or co-surfactant contributes to a greater degree for drug solubilization, more would be the risk of precipitation.
v. The stability of Self nanoemulsifying drug delivery system was affected by temperature and pH.

1.3. Suitable drug candidate identification for Self emulsifying drug delivery system (SEDDS)

For lipophilic drug compounds that exhibit dissolution-rate-limited absorption, SEDDS can offer an improvement in rate and extent of absorption, resulting in reproducible blood time profiles. Logically speaking, however, use of SEDDS can be extended to all four categories of biopharmaceutical classification system (BCS) class drugs [12].

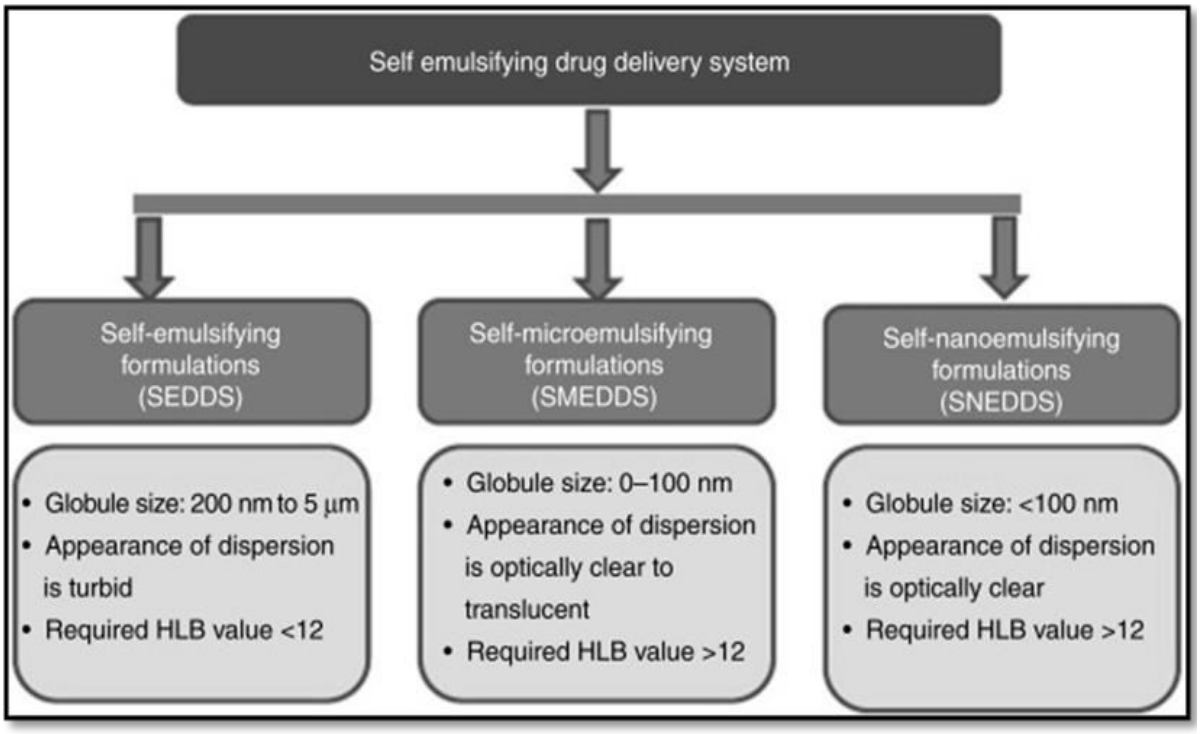

Fig. 1: Difference between SEDDS, SMEDDS and SNEDDS

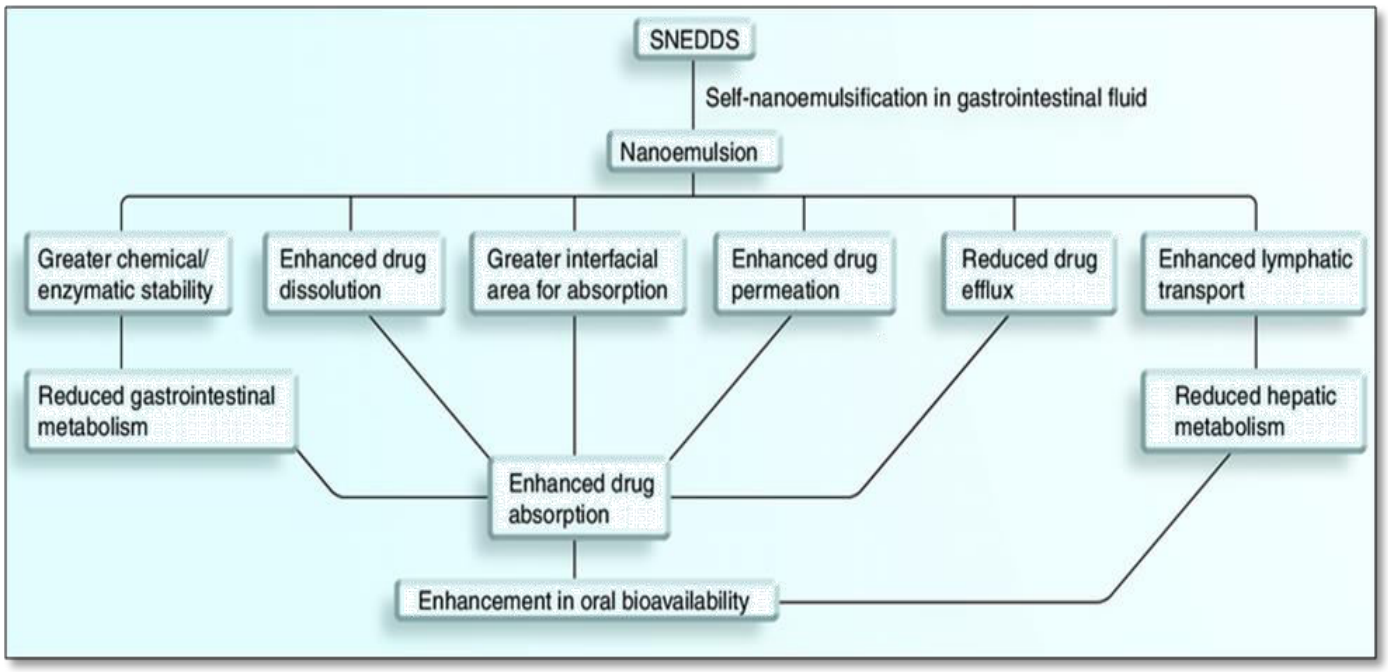

Fig. 2: Potential mechanisms of improvement of oral bioavailability by SNEDDS

1.4. BCS Classification

According to BCS, drug substances or APIs are divided into high/ low solubility and permeability classes as follows:

- Class I : High Solubility - High Permeability
- Class II : Low Solubility - High Permeability
- Class III : High Solubility - Low Permeability
- Class IV : Low Solubility - Low Permeability

In combination with the dissolution, the BCS takes into account the three major factors governing BA, viz. dissolution, solubility and permeability. This classification is associated with drug dissolution and absorption model, which identifies the key parameters controlling drug absorption as a set of dimensionless numbers [13].

Absorption number, An = mean residence time/mean absorption time

Dissolution number, Dn = mean residence time/mean dissolution time

Dose number, Do = (maximum dose strength/250)/ solubility

Class I drugs exhibit a high absorption number and a high dissolution number. The rate-limiting step is drug dissolution and if dissolution is very rapid then gastric emptying rate becomes the rate-determining step. Class II drugs have a high absorption number but a low dissolution number. *In vivo* drug dissolution is then a rate-limiting step for absorption except at a very high dose number. The absorption for Class II drugs is usually slower than Class I and occurs over a longer period of time. In the case of Class III drugs, permeability is a rate-limiting step for drug absorption.

	High solubility	Low solubility
High permeability	**Class-1 (Amphiphilic)** Diltiazem Labetolol Captopril Enalapril Metoprolol Proranolol Phenylalanine Antipyrin **1** Glucose L-Dopa	**Class-2 (Lipophilic)** Flurbiprofen Naproxen Diclofenac Piroxicam Carbamazepine Phenytoin Verapamil Ketoprofen **2** Desipramine Itraconazole
Low permeability	**Class-3 (Hydrophilic)** Famotidine Cimetidine Ranitidine Hydrochlorothiazide Atenolol Acyclovir **3** Nadolol	**Class-4** Terfenadine Furosemide Cyclosporine **4**

Fig. 3: Examples of BCS class drugs

These drugs exhibit a high variation in the rate and extent of drug absorption. Because the dissolution is

rapid, the variation is attributable to alteration of physiology and membrane permeability rather than the dosage form factors. Generally, Class IV drugs exhibit problems for effective oral administration [14-19].

1.5. Mechanism of Self emulsification

According to Reiss; self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required to create a new surface between the oil and water [20].

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

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

The two phases of emulsion tend to separate with time to reduce the interfacial area and, subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence [21, 22]. In case of self-emulsifying system, the free energy required to form the emulsion is either very low or positive or negative then, the emulsion process occurs spontaneously [23].

Emulsification require very little input energy, involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing [24]. Emulsification can be associated with the ease by which water penetrates into the various liquid crystals or phases get formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to the water results in the interface formation between the oil and aqueous continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface, which occurs until the solubilization limit is reached close to the interface [25].

Further, aqueous penetration will result in the formation of the dispersed liquid crystalline phase. As the aqueous penetration proceeds, eventually all materials close to the interface will be liquid crystal, the actual amount depending on the surfactant concentration in the binary mixture once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self- emulsification process causes interface disruption and droplet formation. The high solubility of these self-emulsified systems to coalescence is considered to be due to liquid crystal interface surrounding the oil droplets [25].

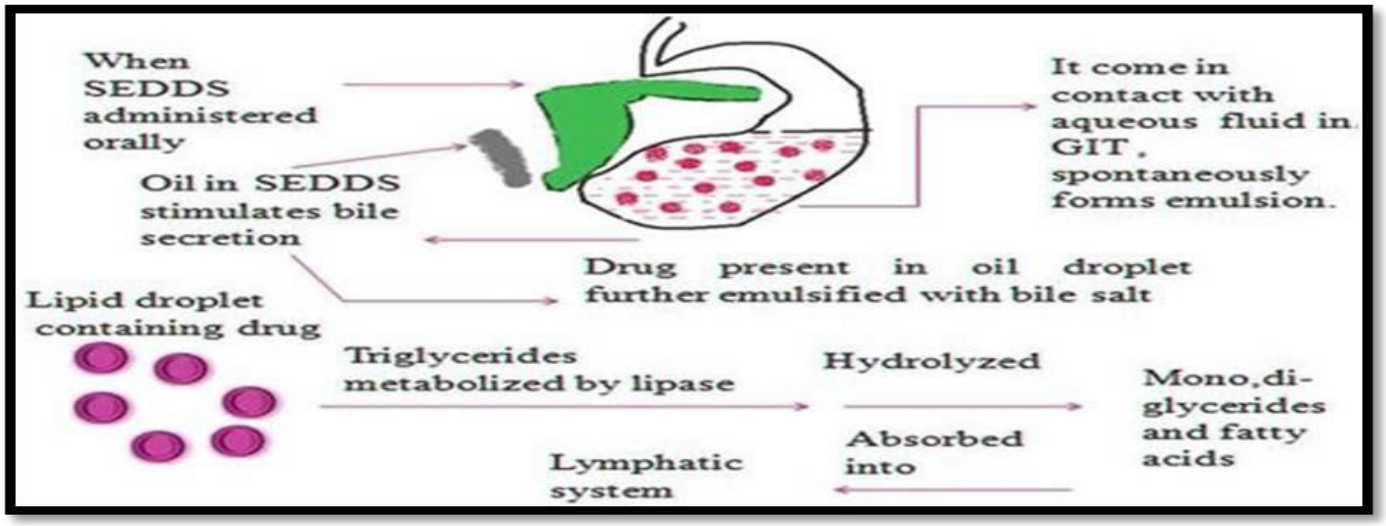

Fig. 4: Process of absorption of self emulsifying drug delivery system

2. FORMULATION COMPONENTS OF SNEDDS

2.1. Oil

In self Nanoemulsifying drug delivery system (SNEDDS) selection of specific oily phase is very important parameter for selection of ingredients in Nanoemulsion, it is mainly associated with O/W nanoemulsion. The oil is important for maximum solubilizing ability for selected drug candidate for selection of oily phase for Nanoemulsion Formulation. This is most important approach having the high drug

loading ability. The naturally as well as synthetically occurring the mixture of oils and fats are triglycerides containing long chain fatty acids. The Triglycerides classified as short chain Triglycerides (<5 carbons), medium chain Triglycerides (6-12 carbons atoms), or long chain Triglyceride (>12 carbons) are important to decrease the degree of unsaturation and are important to prevent oxidative degradation. The choice of oily phase depends on the ability of the solubilized drugs and it is important to form nanoemulsion of desired characteristics. The oil is important to increases friction to transport of drug into intracellular compartment to increases water solubility of less water soluble drug. For example, the mixture of fixed oil and medium chain triglycerides is important to maintain appropriate balance between loading capacity of drug and emulsification or Nanoemulsification. The long chain and medium chain triglyceride oil under different degrees of saturation is important to use in designing of SMEDDS. Triglycerides are highly lipophilic oily molecules and the solvent capacity of drugs is common function of effective concentration in ester groups, the medium chain triglycerides (MCT) molecules having higher solvent capacity and ability for resistance to oxidation as compared to long chain triglycerides molecules. Now days, the MCT have been replaced by novel semi-synthetic MCT to influence water solubility of poorly soluble drugs. Oil phases are modified by vegetable oils, digestible or non-digestible oils and fats such as olive oil, palm oil, corn oil, oleic acid, sesame oil, soybean oil, hydrogenated oil for better solubility [26].

2.2. Surfactant

Surfactants are molecules and ions which are adsorbed at interface. It has ability to prevent the interfacial tension and provide interfacial area. It is major component for preparation of nanoemulsion. It act as self Nanoemulsifying, self-emulsifying and self Micro emulsifying agent and has ability to solubilize poorly water soluble drug. Most of the compounds show the properties of surfactants for designing of emulsifying system. The limited surfactant unit is orally acceptable. Non- ionic surfactants have high Hydrophilic and Lipophilic Balance (HLB). The most commonly used Surfactants are various solid or liquid ethoxylated polyglycolyzed glycerides and polyoxyethylene sorbitan monooleate. Optimum amount of surfactant unit is used for preparation of nanoemulsion as large quantity of surfactant can cause chemical toxicity. Hence, the safety is major considerable parameter for selection of Surfactant molecule. The molecule of surfactant can be of natural as well as synthetic origin [27].

The Non-ionic surfactants are more stable as compared to Ionic surfactants and they are nontoxic and thermodynamically stable molecule. The lipid mixture of molecules with higher surfactant and co-surfactant and oil in a ratio lead to the formation of SMEDDS and SNEDDS and is responsible for enhancement of oral bioavailability of poorly water soluble drugs. The surfactant concentration is mainly based on the Size of droplet molecule for preparation of emulsification and nanoemulsification. This is important for stabilization of oil Droplet under part of surfactant system. The surfactant concentration mainly depends on size of droplet. As the surfactant concentration increases ultimately size of droplet also increases. It is important component of preparation of Nanoemulsion system for improving the solubility of poorly water soluble drugs [28].

2.2.1. Classification surfactant molecule [29]

Surfactant molecule is mainly classified into four types as discussed below:

2.2.1.1. Anionic Surfactants

These are a hydrophilic group that carries a negative charge.

The negative charged groups include carboxyl (RCOO-), sulphonate (RSO_3^-) or sulphate ($ROSO_3^-$). Examples - Potassium laurate, sodium lauryl sulphate.

2.2.1.2. Cationic surfactants

These are a hydrophilic group that carries a positive charge. Example - quaternary ammonium halide.

2.2.1.3. Ampholytic surfactants/Zwitter or Zwitterionic surfactants

The surfactant unit consist of both charges Positive as well as negative Charge. Example - sulfobetaines.

2.2.1.4. Non-ionic surfactants

The hydrophilic group carries no charge but derives its water solubility because it contains strong polar functional groups such as hydroxyl or polyoxyethylene (OCH_2CH_2O). Examples - Sorbitan esters (Spans), polysorbates (Tween 20).

2.3. Co-surfactant

In SNEDDS, generally cosurfactant of HLB value 10-14 is used. Hydrophilic co-surfactants preferably alcohols

of intermediate chain length such as hexanol, pentanol and octanol which are known to reduce the oil water interface and allow the spontaneous formulation of nano emulsion, are used in formulation of SNEDDS [30].

2.4. Co-solvents

Co-solvents may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base which are as follows diethylene glycol, mono-ethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, etc. [30].

3. APPROACHES FOR PREPARATION OF NANO EMULSION

3.1. High energy approach

For the formation of nanoemulsion high energy is applied and is mainly based on the selected composition of mixture, and also on the mixture containing surfactant, cosurfactant, cosolvents and other functional compound. The emulsification undergoes mechanical processing to from nanoemulsion [31].

3.1.1. High Pressure Homogenizer

It is one of the important devices for detection and preparation of fine emulsion, mainly to produce nanoemulsions. This method is important in which the oil/water surfactant mixture under very high pressure and the mixture was pumped by resistive valve. The very high shear stress is responsible for the formation of very fine emulsion droplets. The combination of the two theories, turbulence and cavitation, explains about the droplet size reduction during homogenization process. The high velocity of resultant mixture gives the liquid high energy in the homogenizer valve and generates intense turbulent eddies of the same size as a mean diameter droplet (MDD). Droplets were apart from Eddie currents resulting in a reduction in droplet size. Simultaneously, the pressure drop across the valve, cavitation occurs and generates further eddies disruption droplets. Decreasing the gap size ultimately increases the pressure of the droplet, and is responsible for greater degree of cavitation. Emulsion droplet having diameters < 100 nm can be produced using this method if the sufficient amount of surfactant present to completely cover the mixture of oil-water interface formed and the adsorption kinetics was high, is important to prevent droplet coalescence [31].

3.1.2. Microfluidizatiion

It is an important method to detect and prepare nanoemulsion. The Micro fluidization is achieved by a device called Micro Fluidizer. This type of device is used in high pressure positive displacement pump (500-300 PSI) which forces the product through the interaction chamber, which consists of small channel droplets, called micro channels. The product flows through the micro channels onto the impingements area which results in very fine particles of submicron range i.e. Nanoemulsion. The two solutions containing mixture of aqueous phase and oil phase system are under combination and are formed in the inline homogenizer to yield a coarse emulsion. The coarse emulsion under processing of a micro fluidizer and it undergoes further processing to from homogeneous, transparent and stable nanoemulsion [32].

3.1.3. Sonication Method

It is important for determination of size of droplet and it is important for reduction of droplet size of conventional emulsion with the help of sonication mechanism. It is only applicable for small batches of nanoemulsion [32].

3.2. Low energy approach

It is also called the condensation method, require low energy for the fabrication of nanoemulsions and is based on the phase transitions taking place during the emulsification process.This method mainly dependent on modulation of interfacial phenomenon or phase transitions and intrinsic physicochemical properties of the surfactants, co-surfactants and oil to yield nano-sized emulsion droplets. The low energy method is interesting as it utilizes the stored energy of the system to form smaller droplets. This emulsification can be brought about by the changes in parameters which may affect the hydrophilic lipophilic balance (HLB) of the system like temperature, composition, etc. The most commonly used low-energy emulsification methods are as follows [33]:

3.2.1. Phase Inversion Temperature (PIT) method

It is an important method for preparation of nanoemulsion and micro emulsion. The method is mainly based on the response to temperature. In this type of method many physical changes occur that include physicochemical changes, particle size and *in vivo - in vitro* drug release rate. These methods also make use of the change in spontaneous emulsion formation. The non-ionic surfactant can be achieved by changing the temperature of the system. The forces in transition forms, O/W nanoemulsion at low

temperature and W/O nanoemulsion at higher temperature [33].

3.2.2. Solvent displacement method

Solvent displacement method for spontaneous fabrication of nanoemulsion has been adopted from the nano precipitation method used in polymeric nano-particles. In this method, oily phase is dissolved in water-miscible organic solvents, such as acetone, ethanol and ethyl methyl ketone. The organic phase is poured into an aqueous phase containing surfactant to yield spontaneous or rapidly forming nanoemulsion by the occurrence of rapid diffusion of organic solvent. The organic solvent is removed from the nanoemulsion by a suitable means, such as vacuum evaporation [33].

3.2.3. Phase Inversion Composition Method (Self-nanoemulsification Method)

It generates nanoemulsions at room temperature without the use of any organic solvents and heat. Forgirani et al. in their study observed that kinetically stable nanoemulsions with smaller droplet size (~50 nm) can be generated by the stepwise addition of water into solution of surfactant in oil, with gentle stirring and at constant temperature [6]. Although the components used in the above investigation were not of pharmaceutical grade, and it has opened doors to design pharmaceutically acceptable nanoemulsions using the similar approach [33].

4. FORMULATIONS OF SNEDDS

Successful formulation of SNEDDS requires thorough understanding of the spontaneous nanoemulsification process and also on the physicochemical as well as biological properties of the components used in the fabrication ordevelopment of SNEDDS. The factors influencing the phenomenon of self nanoemulsification are:

- The physicochemical nature and concentration of oily phase, surfactant and cosurfactant or solubilizer (if included) ;
- The ratio of the components, especially oil to Smix ratio (surfactant :cosurfactant) ;
- The temperature and pH of the aqueous phase where nanoemulsification would occur;
- Physicochemical properties of the drug, such as hydrophilicity and lipophilicity, pKa as well as polarity.

The above stated factors should be given attention while formulating SNEDDS. In addition, the acceptability of the SNEDDS components for the desired route of administration is an important factor in the formulation of SNEDDS.

4.1. Steps for formulation of SNEDDS in brief

- Selection of oil, surfactant and co-surfactant on the basis of drug compatibility and solubility study.
- Construction of pseudo-ternary phase diagrams. Selecting ratio of surfactant/co-surfactant and oil on the basis of pseudo ternary phase diagrams.
- Optimization of SNEDDS formula.
- Evaluation of Liquid SNEDDS.
- Selection of best formulation from different formulation of SNEDDS based on data obtained after evaluation studies.
- Conversion of the optimized formulation to solid by adsorbing it on an absorbent carrier.
- Evaluation of solid SNEDDS.

5. CONSTRUCTION OF PSEUDO TERNARY PHASE DIAGRAM

This is the first step before starting the formulation. It is useful to identify best emulsification region of oil, surfactant and co-surfactant combinations. Ternary phase diagram of surfactant, co-surfactant and oil will plot; each of them, representing an apex of the triangle. The methods are used to plot ternary phase diagrams are namely Dilution method and Water Titration method [34].

Psedoternary phase diagram is important for determination of self Nanoemulsifying drug delivery system (SNEDDS). It is diagrammatic representation of oil, surfactant and co-surfactant (Smix), water is known as Psedoternary phase diagram. Psedoternary phase diagram is constructed by Phase titration method and Phase inversion method. The procedure consisted of preparing solutions containing oil and the different ratio of surfactant to co-surfactant by weight such as 1:1, 2; 1, 3:1 etc, these solutions are then vortexed for 5 min and isotropic mixture is obtained and is observed for their appearance (turbid or clear). Turbidity of the samples would indicate formation of a coarse emulsion, whereas a clear isotropic solution would indicate the formation of a Nanoemulsion (SNEDDS) Percentage of oil, Smix and water. The values are used to prepare Pseudo ternary phase diagram. This diagram corner can represent 100% concentration of each phase content.

The diagram is important to give information related to binary mixture of two components such as surfactant/ co- surfactant, water/drug or oil/drug [35].

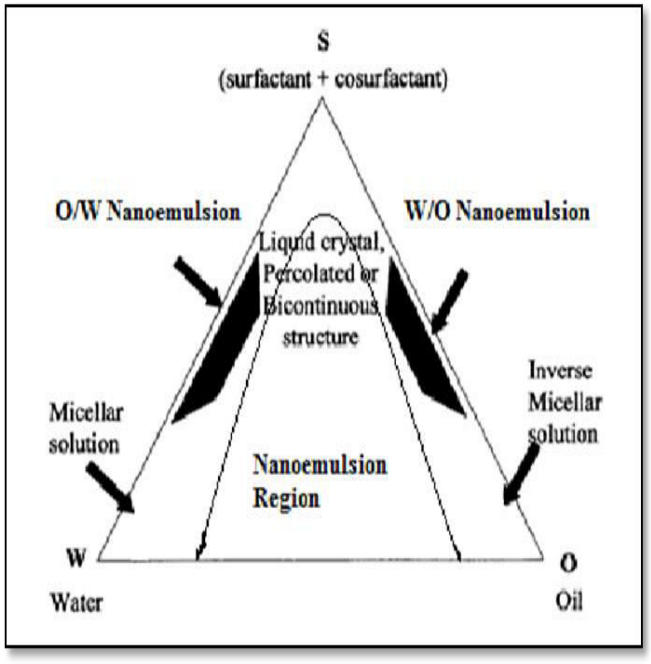

Fig. 5: Pseudoternary phase diagram

6. CONSTRUCTION OF PSEUDO TERNARY PHASE DIAGRAM

6.1. Steps for formulation of SNEDDS in brief

The thermodynamic stability of lipid based formulation is also crucial to it performance, which can be adversely, affected by precipitation of the drug in the excipients matrix. In addition poor thermodynamic stability can lead to phase separation of the excipients affecting not only formulation performance as well as visual performance [36].

6.2. 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 [36].

6.3. Heating and cooling cycle

Three heating/cooling cycles ranges between 4°C and 40°C with storage at each temperature for not less than 24 hr. The resultant formulations were assessed for their thermodynamic instability like phase separation and precipitation. Formulation which passes this test is subjected for further tests [36].

6.4. Freeze thaw cycle

Freeze thawing was employed to evaluate the stability of SNEDDS. Formulations were subjected to 3 freeze-thaw cycles, which included freezing at -4°C for 24 hr followed by thawing at 40°C for 24 hr. Centrifugation was performed at 3000 rpm for 5 min. The formulations were then observed for phase separation. Smix concentrations were optimized formulation [36].

6.5. Viscosity

The Viscosity (rheological property) of the self nanoemulsifying drug delivery system (SNEDDS) was evaluated by Brookfield Viscometer for Determination of Consistency of Nanoemulsion Formulation [37].

6.6. Morphological study

Morphological study is important to give information related to the external appearance of the formulation like colour, odour, consistency, density, appearance was determined by Morphological study. In self-Nano emulsifying drug delivery system (SNEDDS) globules was observed by transmission electron microscope (TEM) Sample was visualized and detected [38].

6.7. pH Measurements

The pH of Nanoemulsion formulations was measured by a pH meter or Potentiometer. Electrodes were completely dipped into the semisolid or liquid formulations and pH was noted [39].

6.8. Percent Transmittance

The percent transmittance of the nanoemulsion Formulation (SNEDDS) was measured using UV-Visible double beam spectrophotometer or Single Beam Spectrophotometer keeping distilled water as blank at 560 nm [40].

6.9. Zeta Potential

Zeta potential is used to identify the charge of the oil droplets of SEDDS. The charge of the oil droplets in conventional SEDDS is negative due to the presence of free fatty acids. For the droplets in SEDDS emulsions, a high zeta potential will confer stability and long shelf life. When the potential is low, attractive forces may exceed this repulsion and the emulsion may break and aggregate. Some investigators consider zeta potential as secondary characterization parameter for SEDDS,

because SEDDS are preconcentrate mixture of drug in oil and surfactant and emulsified *in vivo* only. The zeta potential of SEDDS emulsion is commonly investigated using Malvern Zeta Sizer and the zeta potential values are calculated using Smoluchowski equation [41].

6.10. Self-Emulsification Time

The self- emulsification time is determined by using USP dissolution apparatus 2 at 50 rpm, where 0.5 g of SEDDS formulations is introduced into 250 ml of 0.1N HCl or 0.5% SLS (Sodium Lauryl Sulphate) solution. The time for emulsification at room temperature is indicated as self- emulsification time for the formulation [42].

6.11. Dispersibility Test

The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and categorize the size of resulting globules. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). One ml of each formulation is added to 500 ml of water at 37±0.5°C and the paddle is rotated at 50 rpm. On titration with water, the SEDDS formulation forms a mixture or gel which is of different type depending upon which the *in vitro* performance of formulation can be assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) nano-emulsion, 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 min.

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

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Grade A and Grade B formulation will remain as nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation. The stability of the formulation decreases from micro emulsion to emulgel [42].

6.12. Refractive index

Refractive index is useful to determine the transparency of formulation. The refractive index of the system is measured by refractometer by placing drop of solution on slide and compared with water (1.333). If refractive index of system is similar to the refractive index of water (1.333), then formulation is of transparent nature [43].

6.13. Drug Content

SNEDDS containing drug was added in volumetric flask containing methanol. The mixture was stirred vigorously for 2 hr. The sample was analysed for drug concentration after suitable dilution using UV-spectrophotometer [43].

6.14. Emulsion Droplet Size

The average droplet size is a decisive factor in self-emulsification performance because it will determine the rate and extent of drug release, as well as the stability of the emulsion. Dynamic light scattering (DLS) techniques, photon correlation spectroscopy and microscopic techniques are mainly used for the determination of the emulsion droplet size and Polydispersity index. DLS is ideal for measuring particles or droplets in the diameter of 3 nm to 3 mm. Droplet size distributions can be further verified by cryogenic transmission electron microscopy (cryo-TEM), which offers the possibility to observe the droplet's size and shape. The poly dispersity index of SNEDDS reflects the uniformity of particle diameter and can be used to depict the size distribution of nano emulsion droplets [43].

6.15. *In Vitro* Dissolution

The *in vitro* dissolution studies were performed to evaluate the release efficiency of the optimal formulations. Based on the drug content determinations, self nanoemulsifying formulations were filled in hard gelatin capsule shells. The dissolution was carried out using dissolution test apparatus USP Type II with a paddle stirrer, maintained at 37±5°C, 50 rpm paddle speed. Dissolution was performed in two different mediums viz. 0.1N HCl (Simulated gastric fluid) and 6.8 pH Phosphate buffer 900 ml. The samples were withdrawn at predetermined time intervals and were analyzed for drug concentration by UV-Visible spectrophotometer after filtration through 0.22 μ filter [43].

7. LIMITATIONS OF LIQUID SNEDDS

Self-nanoemulsifying drug delivery systems, being liquid in nature, need to be delivered through either soft/hard gelatin or hydroxypropylmethyl cellulose capsules. There are few issues associated with these systems when presented in capsules, such as incompatibility of

components with the capsule shell in the long term, precipitation of drugs during fabrication and storage at low temperature and critical method of production, among others [44]. In addition, SNEDDS may not be useful for hydrophobic drugs that can undergo pH catalyzed or solution-state degradation.

8. SOLID SNEDDS

The researchers realized that it may be possible to obviate disadvantages associated with liquid SNEDDS handling, manufacturing and stability should one convert them to solid state. Hence, the concept of solid SNEDDS was developed. Solid SNEDDS in the form of dry, solid powders would help in overcoming the limitations associated with liquid SNEDDS. Solid dosage forms are most stable and are convenient for handling; therefore, attempts are made to convert the liquid systems into solid SNEDDS. Various techniques, such as spray drying, freeze drying and adsorption on carriers, can be employed to convert liquid SNEDDS into solid SNEDDS compressed into tablets. The selection of a particular process for preparation of solid SNEDDS would depend on the content of oily excipient of the formulation, properties of active pharmaceutical ingredients, such as solubility, heat stability and compatibility with other ingredients [45].

The simplest technique to convert liquid SNEDDS to solid SNEDDS is by adsorption onto the surface of carriers or by granulation using liquid SNEDDS as a binder. This technique is uncomplicated, cost effective, easily optimized and industrially scalable. It can be used for heat- and moisture-sensitive molecules, thus providing an advantage over other techniques, such as spray drying and freeze drying. Various excipients utilized for the preparation of solid oral dosage forms can be employed for adsorption. The excipients should possess large surface areas to adsorb sticky and sometimes viscous oily SNEDDS formulation [45].

8.1. Characterization of solid SNEDDS

As the final dosage form of the solid SNEDDS is a tablet or a capsule, the powder properties of the solid emulsion particles are important. The nature and the quantity of liquid SNEDDS adsorbed on the surface of a particular excipient would influence the properties of the obtained solid particles. The ratio of liquid: adsorbent quantity is important. Powder properties, such as density, angle of repose, flow, compressibility index and particle size distribution, are important for processing into dosage form. The globule size of spontaneously formed nanoemulsion would govern its performance *in vivo*. The desorption of SNEDDS from the surface of the solid particles and its conversion into nanoemulsion is the rate-limiting step for the dissolution and absorption of the drug. The globule size of the nanoemulsions increases after dispersing the solid nanoemulsifying particles in water. Increase in size is not only related to the carrier used but also to the composition of SNEDDS and properties of the drug. It is necessary to carry out physical characterization of the solid SNEDDS using x-ray diffraction spectroscopy, differential scanning calorimetry and scanning electron microscopy to ensure there is no drug precipitation during preparation of solid SNEDDS. The absence of characteristic drug melting endotherm in differential scanning calorimetry suggests that the drug is in a solubilized state in solid SNEDDS. X-ray diffraction is a useful technique employed in the characterization of crystalline materials. The formation of a diffuse diffraction pattern and the disappearance of characteristic drug peaks indicate that the drug is in a solubilized state in solid SNEDDS. Scanning electron microscopy is useful to investigate the surface properties of the particles and their physical form. *In vitro* dissolution studies would give an idea about the fate of the formulation in the GI tract [45].

9. CONCLUSION

Drug discovery programs yield a large proportion of new chemical entities that are lipophilic and poorly soluble. Self-nanoemulsifying formulations have shown tremendous potential in improving the bioavailability of such therapeutic agents with limited aqueous solubility. The nanosize of these formulations is responsible for facilitating enhancement of drug dissolution and absorption, owing to the large surface area. The lipidic nature of these systems allows delivery of drugs to the lymphatic system. However, certain issues, such as drug-excipient interaction, oxidation of vegetable oils, toxicity and safety warrant attention during the development of SNEDDS. The amenability of converting SNEDDS into solid self-nanoemulsifying systems enables development into solid dosage form. Thus, the solid self-nanoemulsifying system can serve as platform technology for delivering poorly soluble drugs.

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11. FUTURE PROSPECTIVE

Research on SNEDDS technology has accelerated in the last few years and several reports on primary exploration of SNEDDS for the enhancement of oral bioavailability have appeared in the literature. Factorslike pHcatalysed and solution state degradation of drugs in SNEDDS needs to be evaluated. The conversion of liquid SNEDDS to a solid state such as granules, tablets, capsules or pellets with no or moderate effects on the *in vivo* behavior of SNEDDS can reduce the chances of drug degradation as it may not be fruitful in many cases. Thus, it is important to identify microenvironment modulation strategies employed for improving the stability of pH sensitive drugs. It may also be possible to develop controlled release SNEDDS by suitable variations in the composition or fabrication process of tablets or granules. However, it is also necessary to identify a potential highly porous amphiphilic carrier that can convert liquid SNEDDS into a solid powder without causing any significant increase in the volume or bulk density. The applications of SNEDDS in other routes of delivery apart from the oral route should also be needed to be explored. Thus, the commercialization of SNEDDS would be a breakthrough in the drug delivery.

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