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Galvanizing Herbal Delivery by Self-Nano Emulsification

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ABSTRACT
Self Nano-emulsifying drug delivery system (SNEDDS is one of the novel drug delivery systems which help in improving the rate of solubility of inadequately aqueous soluble drugs. SNEDDS are thermodynamically and kinetically durable preparations which involve the isotropic admix of oil, surfactants, co-surfactants, solvents/co-solvents and water. This review explores the potentiality of SNEDDS to upgrade the oral bioavailability of herbal preparations. Many herbal and ayurvedic extracts do not possess ample solubility in water and traditional herbal based preparations such as pastes, creams, pills, ointments did not address the solubility problem. By using SNEDDS and by judiciously blending required excipients the solubility of herbal based preparations can be enhanced significantly. Quality by design (QbD) approach of SNEDDS with respect to herbal based preparations is appraised with relevant examples. The techniques to formulate SNEDDS are reviewed with emphasis on herbal preparations. Evaluation tests of SNEDDS are also discussed. The review concludes by reinforcing the belief that the application of SNEDDS to herbal based preparations offers a promising scope for enhancing the solubility of herbal based preparations.
Keywords: *SNEDDS, herbal, bioavailability, solubility, QbD, stability.*

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INTRODUCTION

Nanotechnology, in the realm of drug delivery, is distinguished as a section of science and technology that addresses the procedures, products and systems to treat medical disorders at a nanoscale. It is continuously enlarging its applications in a variety of medical and pharmaceutical vistas. The classification of nanoscale drug delivery is generically distributed as lipophilic, inert, polymeric Nano carriers, Nano particles as well as Nano suspensions. The nanoscale innovation such as lipoidNano carriers encompasses Nano emulsions as a low energy emulsification method which have been augmented into self Nano or impulsive emulsification methods. Self Nano emulsifying drug delivery system (SNEDDS) are the anhydrous formulations with homogenized liquid admixtures which incorporate elements such as oil, drug, surface active agents, water and organic solvents to manifest transparent Nano emulsion impulsively and upon aqueous dilution with gentle agitation. Ordinarily, the droplet size gained is in the ambit of 20-200 nm.

Roughly forty percentof the new chemical entities (NCEs) demonstrate inferior water solubility, which is preponderantly associated with diminished bioavailability as well as steep intra and inter-patient variance. SNEDDS offers a robust substitute for more traditional oral compositions of lipotropic drugs. The system is proposed to be self emulsifying and it is supposed to be emulsified rapidly in the contents of stomach. Herein, it presents the drug in Nano sized oil beads. These droplets so developed will be evacuated speedily from the stomach which facilitates in swift release of the drug throughout the gastrointestinal route. There are added gains of SNEDDS such as it yields superior interfacial area for distribution of the drug across water and oil which contributes to the ease of dispersion formation when contrasted with that of other normal oil solutions. When contrasted with the fatty solutions, SNEDDS do not rely upon the activities of enzymes, biliary salts or additional effects which are correlative to the fed and fasted status of stomach and curtail the unpredictability in the pace and degree of absorption as well as render further reproducible blood levels. There are some more advantages of SNEDDS when contrasted with other normal Nano emulsions demonstrable increase in the chemical cum physical stability of the formulation alongside the functionality to pack them into the unitized dosage formulations as soft or hard gelatin capsules which expands their marketable cost-efficiency, patient-compliance and ameliorates the palatability associated apprehensions [1].

SNEDDS offers greater benefits over other solubility augmentation techniques such as salt formation as salt creation of neutral substances is not tenable and the production of both weak acidic and alkaline salt products might not be viable. In particular, the salts which are developed may flip back to their primary acid or base manifestations and cause clumping in the gastro-intestinal area (GIT), manifesting in impaired absorption. Secondly, the salts demand excess disbursal of profits such as processing charges [2].

The use of the lipid excipients in various formulations, most probably in case of Nano emulsion such as self emulsifying formulations based on their potential to solubilize less water soluble drugs (lipophilic drugs) has led to both an evolving awareness and achievement over the problem of various factors such as poor drug bioavailability and absorption rate. Conventional micro emulsions as well as Self-emulsifying systems have also materialized as emerging solubility technologieswhose solubilizing and absorption-enhancing role is assumed to be embedded in the reactivity of triglycerides as well as surfactants with gastrointestinal wall permeability. Traditionally, triglycerides of long chain length and triglycerides of medium chain length (LCTs and MCTs, respectively) are used with surfactants to incorporate medications into self-emulsifying structures. Some nonionic surfactants and amphiphilic surfactants require higher degrees of solubilization of the product and avoid micro emulsion (in vivo) precipitation of the product and the most widely used surfactants are nonionic surfactants such asTweens (polysorbates) and labrafil (poly-oxy-ethylated oleic glycerides) with strong hydrophilic-lipophilic balance (HLB) are commonly used to insure that O/W droplets are immediately formed during processing. Many of the co-surfactants utilized include polyethylene glycol, glycerol, propylene glycol, cremophor EL and ethanol, as well as organic solvents that are also included in the preparation to maximize the volume of product that is capable of dissolving into the lipoid base. The bulk of the self-emulsifying system has the excess concentration approaching 30% w/w which is deemed necessary in the myriad self-emulsifying systems. As the surfactant concentration is essential in most self-emulsifying systems to exceed 30 per cent w / w. The product's nature, is a fluid, as a consequence of which the administration is limited to soft or hard lipophilic gelatin capsules in these formulations. In such cases, there may be a lot of interface between the capsule shell and the filled emulsion and therefore need to be planned to prevent dehydration or movement of the hygroscopic substances in the emulsion from the capsule shell that can break down the emulsion and wreak havoc on the stability of self-emulsifying systems [3].

Enhancing oral bioavailability and drug solubility plays a vital role in the delivery of drugs, particularly in the case of lipid-based drugs that are less soluble and have become one of the promising technologies of the last decade due to the multiple roles played by lipids in increasing oral bioavailability, as well as the solubility and enhancement of lipid-based drugs which also attributes to the development of an innovative drug delivery system. Lipids are known to support the carrying of drugs through the lymphatic route. Developing a variety of systems such as SMEDDS, SNEDDS, solid dispersions, liquid / solid solutions, and physical mixtures depend on the drug delivery system excipients and methods of formulation included. The most feasible pathways for all of these formulations are improved transcellular diffusion by enhancing membrane fluidity and also enhancing para-cellular transmission by opening a close junction and also inhibiting both cytochrome P450 and P-glycoprotein for intracellular concentration enhancement and formatting. SNEDDS analysis of less water-soluble drugs developed and tested for various parameters such as FTIR, *in-vitro* drug release, droplet size and electron scanning microscopy [4].

HERBAL OIL PREPARATIONS

There are numerous preparations of SNEDDS in which herbal oil is used as a drug, some of them are as follows:

Devising Nano emulsion of cinnamon oil:

PreparingNano emulsion is based on the use of cinnamon oil (CO) and cinnamon oil is one of the essential oils which require various modalities such as minimal and maximal energy modalities. There are:

Low energy modality:

- Spontaneous emulsification (SE),
- Emulsion-inversion point (EIP) method
- Phase-inversion composition (PIC) technique
- Phase-inversion temperature (PIT) process

High energy modality:

- Rotor-stator system (RSS),
- High-pressure homogenization (HPH),
- Ultrasound-assisted emulsification (UAE)

- Micro fluidization (MF)

Production of self-Nano emulsification systems basically requires low-energy and high-energy techniques that also include low and high emulsification methods and where both internal chemical energy and mechanical devices are used as above. Low energy is the most appropriate and preferred method, as large volumes of emulsion can be prepared with low processing expenditure.

The methods used to fabricate CO-based Nano emulsions:

The first process used to produce Nano emulsions based on cinnamon oil is ultrasound-assisted emulsification (UAE) at 20 kilohertz and 750 Watts using sonotrode samples in which the ramipril-assisted angiotensin-converting enzyme (ACE) inhibitor and the antifungal drug fluconazole.

Another method used is the Rotor-stator system (RSS) at diverse agitation rates that is 7,000–24,000 rpm and the time required is 2 minutes to 1 hour.

High-pressure homogenization (HPH) at a range of pressures 137.9– 200 MPa and cycles of about three to five is applied for the preparation of coarse and fine cinnamon oil based emulsions.

Micro fluidization (MF) is another method which is used for fabricating CO-based Nano emulsions. To Nano emulsify an oil phase consisting of CO and coconut oil at 900 bar, three passes were performed and it was found that MF when compared to other methods such as RSS, UAE and SE resulted in smaller mean particle size. To achieve stable and ultrafine trans-CIA and CO based Nano emulsions RSS was combined with that of HPH. It generates spontaneous emulsification (SE) for preparing the CO based Nano emulsion because of the mild dispensation conditions and fast formations of the Nano droplets. For the ease and possible formation of the CO based Nano emulsion there must be the formation of continuous phase by rapid molecular movement of both surfactants and solvents from the dispersed phase without any variations in surfactant curvature or phase shift [5].

Preparation of Nano emulsion of eucalyptus oil:

Most of the time there is a use of herbals as the core drug for the preparation of the Nano emulsion where the oil of the drug is extracted and used for the formulation of the Nano emulsion. The extracted oil of the eucalyptus which is the essential volatile oil is used in the preparation of Nano emulsion. The Nano emulsion using eucalyptus oil is O/W emulsion by using non-ionic surfactant such as Tween 80 and water. For the preparation, the concentration for the eucalyptus oil is kept constant that is 6% v/v for all the formulations. At first coarse emulsion was prepared with the addition of water to the organic phase containing eucalyptus oil and surfactant by using various ratios 1:1, 1:2, 1:3 v/v and so on, with the help of magnetic stirrer, further by using 20 kilohertzultrasonicator with the power output of 750 Watts, the crude emulsion is finely emulsified and the energy input was given with the help of sonotrode containing piezoelectric crystal having a 13mm diameter probe. The conversion of the coarse emulsion to the Nano emulsion is by using a Sonicator probe which regulates unsettling forces which helps in reduction of the droplet size or droplet diameter. Further the stability was investigated and the categorization of Nano emulsions was also carried out [6].

Preparation of Nano emulsions:

PreparingNano emulsion of eucalyptus oil along with the excipients is given below in the table. The presence or the absence of the surfactant and co surfactant are the variables that are taken into consideration. He composition of the Nano emulsion is taken as given in the Table 1 and are developed by incorporating drug along with surfactant or fusion of both surfactant and co-surfactant prior to the addition of the requisite quantity of water and the combination of all these was then equilibrated using ultrasonicator for 5-10 minutes [7].

Preparation of Nano emulsion of peppermint oil:

Methods:

Selected as the oil process were peppermint containing oil (PO) and medium-chain length triglycerides (MCT). PO derived from green leaves and *Mentha canadensis L* flowers by steam distillation. The primary product of GC-M is menthol, a terpenoid compound with moderate water solubility.

Preparation of Emulsions:

A Purity Gum 2000 aqueous solution at 12% (w/w) concentration was devised by diffusing the dried powders in de-ionized water at room temperature and keeping it stirred overnight to augment hydration of starch before it is homogenized. Simple PO, MCT and mixture of both, were used as core materials in the given ratio as 1:1, 1:5 and 5:1 (v/v). The lipoidal and water phases were pre-mixed with a fast-speed homogenizer running at room temperature at 24,000 rpm for 1 min. Such crude emulsions were finely spread with a high-pressure homogenizer having pressure of 50, 100 and 150 MegaPascal for 1/3/5/7/ 10/15/20 cycles. A heating exchanger was also utilised during the cycle [8].

Preparing the Nano emulsion of garlic oil:

The formulation of garlic oil containing Nano emulsion was done using the equipment, Shimadzu GCMS-QP2010 Ultra for the processing of garlic oils with GC-MS (Shimadzu Scientific Instruments, Columbia, MD, United States). The scanning rate of 3 scans/second, and a GC-MS solution were applied in the electron impact (EI) type package with 70 eV electron energy to produce Nano-emulsion in garlic oil while propylene glycol used as a co surfactant. Surfactant / co-surfactant blends were blended with predefined ratios at 1:1, 2:1 and 3:1, in glass test tubes with the tops, respectively. Diverse co-surfactant / surfactant blends of 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2 and 9:1 (oil: co-surfactant / surfactant) are added to garlic oil. The surfactant / co Surfactant mixtures were then added on a drop-specific basis in conjunction with the specified weights of oils until a smooth, translucent Nano emulsion had occurred. Methylated Blue and Sudan III were used to evaluate whether O/W or W/O was a Nano emulsion. Garlic oil Nano emulsion was considered W/O because Sudan III, a petroleum-soluble dye, diffused in the Nano emulsion quicker than methylene blue. Conversely, as methylene blue (water-soluble dye) is spread more readily into the Nano emulsion, Nano emulsion was called O/W. A surfactant mixture was found to be the optimal solution for Nano-emulsion: a co surfactant equal to 3:1 and a garlic oil mix: a surfactant and co surfactant mechanistic equivalent of 1:9. Determined retention indices by the homologous n-alkane sequence [9].

Preparation of Nano emulsion of tulsi leaf oil:

Nanoemulsion formulations (NEF) with various ingredients along with Ocimum sanctum oil was prepared as per (Table 2). As stated, the formulations for Nanoemulsion have been prepared with minor changes. For various method formulations (o/w or w/o), the oil was dissolved with the aid of emulsifier. The oil was collected in aqueous phases for the preparation of Nanoemulsion under the emulsion stirrent technique. After the homogenization was stirred, the oil produced in water or gas was deposited in oil Nanoemulsion. Both samples were held at room temperature in Nano emulsion formulations [10].

Preparation of Nano emulsion(NE) of turmeric oil /turmeric extract:

a) Preparation of turmeric extract:

At the onset, turmeric extract (TE) was collected at room temperature by vortexing for 24 hours, turmeric powder in 50% ethanol. The extract was purified and condensed under reduced pressure with the help of spinning evaporator in order to increase its curcumin quality (20 brix). Next, 20% (w/v) dextrin was dried with a hose. Using HPLC process, the final turmeric extract curcumin content was calculated.

b) Solubility of turmeric extract in different oils:

In oleic Acid, olive, grape seed, maize and soybean oils, the solubility of the turmeric extract was estimated. In each liquid, turmeric (1%, w/v) was introduced and magnetically extracted at 60°C for 10 min. At 12,000 rpm, the resultant product was centrifuged to extract unreleased material at room temperature for 10 minutes using a centrifuge (1248R, Gyrozen, Korea). Then further sample was prepared by applying 900 µL of 100 percent DMSO to 100 µL of the TE-NEs and whirling thoroughly to assess the curcumin material. High-performance liquid chromatography (HPLC; Shimadzu D20A, Japan) with an ACE4 C18 (4.6 to 250 mm, 5 microns, Advanced Chromatography Technologies, United Kingdom) and an UV absorption detector were used. Mobile fluid phase with a flowing rate of 1.0 ml per min was acetonitrile and acetic acid of 2% (65.35 v/v). A sample amount of 20 mm, controlled at 265 nm was applied.

c) Preparation of turmeric Nano emulsions (TE-NEs):

There were four formulas generated by changing the surfactant ratios: control (lecithin: 20, 1:1), form-A (lecithin: 20: WPI, 1:1:1), form-B (lecithin: 20: WPI, 0:1:2) form-C (lecithin: 20: WPI, 1:0:2). To prepare the TE-NEs, 1% (w/v) of turmeric extract in soy oleic acid (lipophilic surfactant) was prepared first for the oil Process. The water process was generated by combining with distilled water (Tween 20 is removed in one of the formulations tested) in combination with hydrophillc surfactants such as Tween 20. For 2 hours the combination was magnetically whisked to produce a gritty emulsion. It was initially exposed to high-speed homogenization (HSH), at 5,000rpm for 10 minutes, and eventually ultrasonicated with the aid of Vibra-Cell working at 750 Watts, with an amplitude of 40 to 15 minutes [11].

Materials and methods for general preparation of Nano emulsion:

The materials involved in the development of SNEDDS are the meagerly aqueous soluble drug of (class II and IV)and other excipients or additives such as surfactants of different types they are Anionic surfactants(Potassium Laurate and Sodium Lauryl Sulphate[SLS]), Cationic surfactants(Quaternary Ammonium Halide), Ampholytic surfactant(Sulfobetaines) and Non-ionic surfactants(Sorbitan esters-spans and polysorbates-tween20). Also there is use of other additives which are known as co-surfactants/co-solvents and some of them are Ethanol, Methanol, Pentanol, Glycol, Propylene glycol, Polyethylene glycol, Acetone, Propanol alongside with oil and water.

The Self Nano-emulsifying drug delivery system will be created by various techniques like agitation or by using homogenizer. The less water soluble drugs and the surfactants and co surfactants and co-solvents will be selected based on the obtained results of compatibility study between the active ingredient and surfactants and co-surfactants. Various surfactants and co-surfactants/co-solvents are used such as Spans, Tween20, ethanol, methanol, propanol, glycol, propylene glycol, polyethylene glycol, acetone, alone or in combination, will be tried to obtain the best formulation.

General procedure involved in preparing the self Nano-emulsifying drug delivery system (SNEDDS):

Preparation of selfNano-emulsifying drug delivery system involves various techniques and methods such as homogenization, sonication and phase inversion methods and also agitation method using mortar and pestle. A flowchart of the general procedure for preparing SNEDDS is shown in Fig. 1. There are two types of SNEDDS are prepared they are solid-SNEDDS and liquid-SNEDDS and the procedure for formulatingboth solid-SNEDDS and liquid-SNEDDS are as follows:

Preparation of liquid-SNEDDS:

The preparation of solid-SNEDDS is carried out by taking the ratios of surfactants and co-surfactants as well as oils used by using pseudo ternary phase diagram and then the obtained ratios of each ingredients is selected.Further numbers of series of formulations are prepared using different concentrations of oils, surfactants and co-surfactants.Oils and surfactants are weighed in appropriate properties.The drug is added in the fusion.The combination is kept at room temperature [12].

Preparation of solid-SNEDDS:

The preparation of solid-SNEDDS is carried out once the liquid-SNEDDS are prepared and these prepared liquid-SNEDDS are selected and mixed in the mortar and pestle and then a mass damp is obtained and that mass damp is passed through sieve no.120 and the granules are obtained which is desiccated at normal temperature [12].

Formulation of SNEDDS can be carried out by using:

Various techniques are used for the formulation of the liquid and solid SNEDDS are:

- Homogenizer
- Sonication
- Phase inversion
- Pseudoternary phase diagram

Homogenizer:

The homogenizer is one of the important tools for its generation of for Self Nano emulsifying medicament distribution. This approach is essentially based on the principle that when the O / W surfactant blend is pumped by resistive valve under very high pressure and then blended, the extremely high shear stress ensures that very fine emulsion droplets are formed. The convergence of two hypothetical mechanisms namely, friction and cavitation, describes the decline in the thickness of the droplet. The greater intensity of the subsequent mixing provides strong liquid pressure to the homogenizer valve and creates chaotic edges of the mean diameter droplet MDD size. At the same point, the air rises across the pipe. There is cavitation and extra droplets are produced due to the destruction of eddies. Finally, the gap that is formed ultimately lowers the diameter of the droplet and improves the cavitation. The droplet emulsion measures up to 100 nm in diameter. This technique can be used if the mixture of the existing boundary between oil and water is fully covered by the sufficient surfactant, adsorption kinetics are strong and coalescence is prevented [13].

Example: Two simultaneous homogenization methods are used for the preparation of BCS class 4 drug O/W Nanoemulsion using 5% Triolein (having 4.45% medication) homogenizing with 95% aqueous (2% Tween-80 and 93% double distillated-water) phase. The first method was to homogenize the solution for a 180-second using Ultra-Turrax T25 at 13,000 rpm. Secondly, it was necessary using a standardizing high pressure bench homogenizer with a pressure of 800 bars for the 5 cycles, to subjugate the pre-prepared emulsion to a high-pressure homogenization process. The nanoemulsion was made cooler than 25°C to prevent the oxidation of bioactive agents with an ice bath after each homogenization process. The Triolein emulsions devoid of drug were also developed for comparative purposes [14].

Sonication:

The sonication approach is one of the essential means of determining the globule size and, with the support of the sonication system, it is critical for the globule size of traditional emulsion. This is only sufficient for small quantities of nano emulsion [15].

Example: Orange oil (sweet), Emulphor 620 (the surfactant), and Capmul (the co-surfactant) were used for dissolving the medication cyclosporine A in oil. QbD method was used to prepare different SNEDDS formulations. The mixture was emulsified by water and ultrasonicated isothermally for about 15min to 1/2 hour in an ultrasonic resonator array. SNEDDS containing multiple oil: surfactant: co-surfactant

ratios were used to calculate sound intensity and absorption rate. Droplets were squeezed, droplet-hydration was known, and rigorous Ultrasonic Methods with a single Resonator Frequency were used to test the effect of the composition on droplet stability. For the liquid, aqueous and system components the adiabeticcompressibilities were 68, 44.6 and 53[10−11/Pa), which were determined using the Urick's equation [16].

Phase inversion:

Phase inversion is an important tool in the design of the drug delivery mechanism for self-nano emulsification. There are many physical changes in the phase inversion process, such as physical transform, different particle sizes and in-vivo, in-vitro release time of medications. The primary basis for this approach is the temperature reaction. This method uses the random forming of emulsions to shift the non-ionic surfactant from one phase to the other which is achieved by increasing the temperature in the device. At low temperature, the transformation from nano-o/w emulsion was forced to w/o and vice versa Nano-emulsion were developed at higher temperature [17].

Example: The emulsified systems are particularly sensitive to the temporal scale for which the dispersed phase in the continuous system was added. There are several experiments through a transitional reverse phase path, often leading to Nano-emulsions and distorting the speed of adding the second-phase (water) to the first-phase (oil). The optimal state was achieved for the emulsification phase if the ideal composition was preserved at a critical stage. A slow introduction to the oil (time > 1 min) allows for the transient reversal and thus the production of sub micrometer droplets.At the very least these two inversion processes led to the creation of the nano emulsion droplets locally and when the effects change or there is a bimodal drop-size spread. The fast introduction of the water phase (<5-10 sec) contributed to the dominant and relatively large droplets of the devastating phase inversion process. The results show that spontaneously generated emulsification is fast, but not instantaneously generated. The scale of the droplet is somewhat influenced by the addition intensity and also by the low surfactant content [18].

The Pseudo Ternary Phase Diagram:

It is the diagrammatic depictions of various elements, in pseudoternary phase diagrams, the elements included are oil, Smix (surfactant and co-surfactant) and water (Fig. 2). The Pseudoternary process is illustrated as a combination of surfactants, co-surfactants, oil and water. It is principal to identify the SNEDDS and to prepare the SNEDDS. It is appropriate to prepare solutions containing oil, surfactant by weight to co-surfactant as 1:1, 2:1, 3:1, etc., and to obtain an isotropic mix for 5-10 minutes. The appearance is observed (turbid or unobtrusive). Turbidity suggests the coarse emulsions produced by the materials, while the transparent isotropic solution shows the production of SNEDDS. The percentage values of oil, Smix and water are used to draw up a diagram of a pseudoternary process. The diagram angle should reflect 100% of the concentration of each step material. The diagram is essential for providing information on the tertiary mixture of all the three components including Smix, water and oil [19].

1. Types of SNEDDS:

There are three types of Self Nano Emulsifying Drug Delivery System (SNEDDS)

- Oil in water (O/W) type of SNEDDS
- Water in oil (W/O) type of SNEDDS
- Bicontinuous type of SNEDDS

O/W SNEDDS:

The oil of the form SNEDDS water is rendered by dispersing the oil process into the aqueous dispersion medium. The formulation comprises of isotropic wax, surfactant, co-surfactant and product mixtures containing delicate oil-in-water nanoemulsion when the isotropic mixture is put into aqueous phases under mild agitation.

Example: Cefpodoxime proxetil (CFP) is orally administered to treat upper region of airway in respiratory tract illnesses and urinary tract infections. The overall bioavailability when supplied as a 130 mg pill that is equivalent to 100 mg cefpodoxime in humans is only about 50%. The SNEDDS formulation approach (O/W) which increases the drug's solubility and bioavailability and protects the drug against degradation of cholinesterase in intestinal washings is highly desirable to improve the therapeutic efficacy of the CFP drug. Unlike other forms, such as SEDDS and SMEDDS, SNEDDS through their anhydrous form are packaged in hard-gelatin capsules hence they are more convenient, more efficient and more patient-friendly for planning the drug delivery device. Studies are being carried out and these trials have been successfully confirmed to deliver a comparatively high dose CFP of the medicine in the SNEDDS unit dosage form [20].

W/O SNEDDS:

The water in oil type of SNEDDS is prepared by dispersing the dispersed phase which is aqueous phase into the dispersion medium which is an oil phase.

Example: Caffeine has been developed in several specific W/O SNEDDS using an oil phase titration process in recent years. Caffeine was recently tested to treat multiple types of cancer when ingested orally, and there is some indication that it protects skin from skin cancer that can be caused by skin exposure to the sun when dermally adding caffeine. The current investigation further formulates and measures the SNEDDS system of caffeine which can be used for the delivery of transdermal drugs. SNEDDS are thermodynamically stable and kinetically robust, with distinctive size, viscosity, refractive index and morphology. Furthermore, studies on in vitro skin permeation of Franz diffusion cells were conducted utilizing rat skin as a permeation membrane. The optimal approach is contrasted with the in vitro skin permeation paradigm by the aqueous solution of caffeine. In comparison to the aqueous caffeine solution, the permeation capacity of the drug by permeation membrane ($P < 0.05$) is considerably improved.For the uniform SNEDDS formulation (C12), stationary flux (Jss) is 147.55 ± 8.21 µg /cm2/h and coefficient permeability (Kp) is 1.475 − 10−2 ± 0.031 ± 10−2 cm/h respectively. These overall results have showed that W / O SNEDDS are transdermally sturdy sources of caffeine [21].

Bicontinuous SNEDDS:

Bicontinuous SNEDDS were made either through the spontaneous emulsification process known as titration, or simply by adding all of the ingredients in the right proportion, including water, oil, surfactant, and co-surfactant, with moderate agitation. The process's behavior tests demonstrate that in the inversion stage, the droplet component is caused by two different ways, either by temperature or composition. This principle is known to be behind nano emulsions. Nano emulsions are often known as mini emulsions, ultrafine emulsions, and internal-phase droplet submicron emulsions have a weight of less than 1000 nm. A co-surfactant that appears to create thermodynamically stable nano-emulsions spontaneously causes low tension of the systems. A study of nano emulsions by reversal method, showed the relationship between the minimum droplet size and the total solubility of the oil in the bicontinuous micro emulsion framework, independent of the initial phase equilibrium, is single or multiphase and the stability of nano emulsions against sedimentation [22] as shown in Table 3 [23, 24].

SIMILARITIES BETWEEN SEDDS AND SMEDDS/SNEDDS: [23]

Form fine oil-in-water dispersion in contact with Gastrointestinal Fluid (GIF) as shown in Table 4.

Evaluation:

There are various evaluation parameters to evaluate the SNEDDS formulation and they are as follows:

- Thermodynamic stability studies
- Centrifugation studies
- Heat-cool cycle
- Freeze thawing cycle
- Droplet size
- Viscosity
- Short term accelerated stability studies
- Drug content
- Dispersibility test
- Morphological study
- pH measurements
- Percentage transmittance

Thermodynamic stability studies:

Also crucial to it performance is the thermodynamic stability of lipoidal formulation, which can be adversely affected by drug precipitation in the excipients matrix. In addition, poor thermodynamic stability of the formulation will manifest as phase separation of the excipients affecting not only the formulation output but also visual performance [25].

Centrifugation:

Formulations were put for centrifuging for 25 min at 3000 rpm and analyzed to different phases. For the heating and cooling cycling, formulations which showed no phase separation supported by visual observation were taken for further studies [25].

Heating–cooling cycling:

Six cycles were conducted between the temperature of the refrigerator (4˚C) to and fro 45˚C in a hot air oven (Micro labs, Mumbai, India) with 48 hour storage at each level, and the formulation which did not reveal turbidity and phase separation at such temperatures was exposed to a freeze thaw cycle [25].

Freeze thaw cycling:

For the formulas between -21˚C and 25˚C these cycles were performed for 48 hours. Another freeze-thaw cycle consisted of storing Nano emulsion for 24 h at-21˚C after they were stored for the next 24 hours at

25 ˚C. Three such freeze thaw cycles were performed and then the Nano emulsion was observed with physical stability. For characterization, the formulations that endured the stability tests were accepted. Compositions of the formulations are selected for Nano emulsion [25].

Droplet size:

Droplet size (SNEDDS) was measured using a Zeta sizer, a photon-interaction spectroscopy that examines the variations in the scattering of light due to Brownian particle motion. The light dispersion is measured at an angle of 90˚ at 25 ˚C in distilled water the engineered SNEDDS sample was dissolved and it was deposited into the quartz cuvette and was exposed for determining the size of the droplet. Droplet size distribution was calculated by photon similarity spectroscopy, using a zeta sizer, which examines the variations in light scattering because of Brownian particle motion. The light dispersion was measured at an angle of 90˚ at 25 ˚C. A laser diode with a solid state was used as source of light. The prepared optimized Nano emulsion sample was sufficiently diluted with distilled water, put in quartz cuvette and subjected analysis of droplet dimension [25].

Viscosity measurement:

The viscosity was measured using a triplicate spindle no. 2(62) of Brookfield viscometer LV DV-E (Brookfield Technology, USA), at 25 ˚C. The viscosity (rheological property) of the SNEDDS is determined by Brookfield Viscometer for SNEDDS formulation and also determination of consistency [25].

Short term accelerated stability studies:

The SNEDDS were inserted into unfilled HGC (size 0) and stability studies were performed at different relative humidity's and corresponding temperatures like 25 °C / 60% relative humidity (RH), 30 °C/65% RH, and 40 °C/75% RH.The different samples were provided with different humidity and temperature control in the stabilization chambers (Thermo lab, Mumbai, India). These were collected for review over duration of 6 months for moderate and advanced conditions at specified intervals, and 12 months for long-term conditions. The capsules' drug content was evaluated using a formerly developed and tested HPLC stability indication system [26].

The Temul, Dnm, DE15min, % transmittance, viscosity, and product quality, the formulations stored in airtight glass vials were routinely checked from 0, 1, 3, & 6 months. Studies of invitro drug release and similarity factor (f2) were performed to recognize some significant changes in the dissolution profiles [27].

Drug content:

Substance is removed from pre-weighed SNEDDS by dissolving it in an acceptable solvent. Drug content in the solvent extract was measured against the drug's normal solvent solution using appropriate analytical process [28].

Dispersibility Test:

A characteristic USP XXII dissolution apparatus of the type II is used to determine the efficacy of self-emulsification of oral nano or micro emulsion. One ml of each formulant was applied at 37±0.5˚C to 500 ml of water. A regular, 50 rpm revolving paddle of stainless steel dissolution produced gentle agitation. The formulations' in-vitro output is measured visually using the grading system and they are as follows:

Grade A: Within or less than 60 second there is a quick formation of blue or clear solution

Grade B:The solution quickly turns into a bluish white color which is slightly clear or transparent

Grade C:Formation of fine milky white emulsion in more than 1minute and within 2 minutes of time

Grade D: It takes more than 2 minutes to form a grayish white emulsion which appears slightly oily and is dull in color

Grade E: The presence of enlarged globules on the surface of an emulsion leads the formulation to be a weak/medium emulsified.

Grade A and B remains as Nano emulsions while that falling in grade C can be suggested for the preparation of SEDDS [28].

Refractive index and Percentage transmittance.

The system's refractive index is calculated by refractometer by putting the solution decline on the slide and contrasting it with water (1.333). The system's percentage of transmittance is calculated at specific wavelength using a UV spectrophotometer that leaves distilled water as null. If the refractive index of the device is close to the water refractive index (1.333) and the formulation has a transmittance percentage of > 99%, the formulation will be visible [28].

Morphological study:

The research was necessary for providing the accurate information which is related to the surface morphology of the prepared SNEDDS such as color, odor, quality, distance, and morphological analysis has defined appearance. Globules were observed and identified in the SNEDDS sample with the help of Transmission Electron Microscopy (TEM) technique.

Morphological and structure analytical evaluation of NRG charged SNEDDS was performed using electron transmission microscopy (TEM, Hitachi, Japan) on a 100 kilovolt point-to - point H7500 resolution unit. A drop (0.5 mL) of the SNEDDS solution was placed directly on the copper electron microscopy grids aided by formvar films, diluted with water at 1:100 intervals. The waste was pulled out using filter material. The grids were then painted with 0.5 per cent aqueous solution of phospho-tungstic acid for 30s, and the surplus was drawn out. TEM was examining the grids when they were drying. The combination of different bright field pictures with magnification have been used to reveal the structure and scale of the Nano emulsion produced [29].

pH measurements:

The pH of formulations of the Self Nano emulsifying drug delivery device was calculated using pH meter/potentiometer. The Electrodes have been fully immersed inside the compositions of semisolids/liquids, pH has been observed.

The pH of the water phase can have important implications for the separation stage and the quality of the self-emulsifying cycle. Selected formulas have been diluted with different diluents (i.e. deionized water, 0.1 N HCl, and phosphate buffer pH 6.8) to this purpose (20 and 1000 times). The distilled formulations were held for 8 h at 25 C, and visually monitored for any indication of phase separation or precipitation of drugs [29].

Solubility studies:

Solubility tests Drug solubility in excipients plays an important role in evaluating drug consistency, since many formulations are precipitated before in situ solubilization. Screening of sufficient oil is therefore a primary requirement for the production of SNEDDS. Similar long chain, short chain, and synthetic triglycerides with similar HLB values were used for solubility determination. The self-emulsifying Nano emulsion should be isotropic, monophasic and should have sufficient solubilizing ability to fit product dose into the minimal formulation length.

Higher drug solubility in oil leads to lower surfactant and co-surfactant requirements which reduce surfactant toxicity. Explained before evolved HPLC approach was used for drug solubility study in excipients. The strong log P value is 5.98 which guarantees a good lipophilicity of the compound, as shown in the results of solubility studies published [30].

Applications: [31]

Novel applications of SNEDDS and current research are as follows:

a. Supersaturated SNEDDS
b. Solid SNEDDS
c. Controlled release solid SNEDDS
d. SNEDDS; as mucus permeation enhancing strategy
e. SNEDDS for the delivery of bio macromolecules
f. Self double nano emulsifying drug delivery system (SDEDDS)
g. Targeted SNEDDS

Table1. Selected Nano-emulsion Formulations %(V/V) [7]

Component	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**
Eucalyptus oil	10	10	10	10	33.33	25
Tween™20	80	40	10	5	33.33	25
Ethanol	**-**	40	-	5	-	25
Water	10	10	80	80	33.33	25

Table 2. Preparation of Nano emulsion formulations

Sl. No	**Types of ingredients**	**%Compositions of Nano emulsions formulations (w/w)**		
		F1	**F2**	**F3**
1	Distilled water	55	50	45
2	Ocimum sanctum	30	25	20
3	Emulsifier	10	15	20
4	Stabilizer	05	10	15
5	Total	100	100	100

Table 3. Difference and Similarities between SEDDS, SMEDDS/SNEDDS [23, 24]

SEDDS	SMEDDS/SNEDDS	Ref no.
SEDDS Self Emulsifying Drug Delivery System	SMEDDS - Self Micro Emulsifying Drug Delivery System SNEDDS - Self Nano Emulsifying Drug Delivery System	(23)
SEDDS are the simple binary formulation which consist of drug and lipid excipients when comes in contact with gastrointestinal fluid it is able to self-emulsify hence known as Self Emulsifying Drug Delivery System.	SMEDDS/SNEDDS are the novel drug delivery system which consists of isotropic mixture of drug, aqueous and non-aqueous excipients.	
SEDDS is a system which comprise of components such as drug, surfactant and oil.	SMEDDS/SNEDDS are the systems which composed or comprise of substancesas drug, aqua, oil, surfactants/co surfactants and solvents/co solvents.	
The size of the lipid droplet in the dispersion and ranging from 200nm-5µm, enlarging the surface area for more absorption.	Size of lipid droplet in the dispersion is almost <200nm which may increase the solubility, bioavailability and the rate of absorption.	
The dispersion or SEDDS has turbid appearance	The dispersion or SMEDDS/SNEDDS has an optically clear appearance	
The system is not thermodynamically stable in physiological condition and water.	SMEDDS/SNEDDS systems are thermodynamically and kinetically stable in water and physiological condition	

Table 4. Difference and Similarities among the Drug Delivery Systems:

Properties	SEDDS	SMEDDS	SNEDDS	Reference no.
Droplet size	>300nm	<250nm	<100nm	[24]
Manifestation	Turbidity	Optical clarity	Optically clear	
HLB of the surfactant	<12	>12	>12	
Categorization as per Lipid formulation categorization system	Type II	Type IIIB	Type IIIB	
Concentration of lipoidal component	40-80%	>20%	>20%	
Concentration of surfactant component	30-40%	40-80%	40-80%	

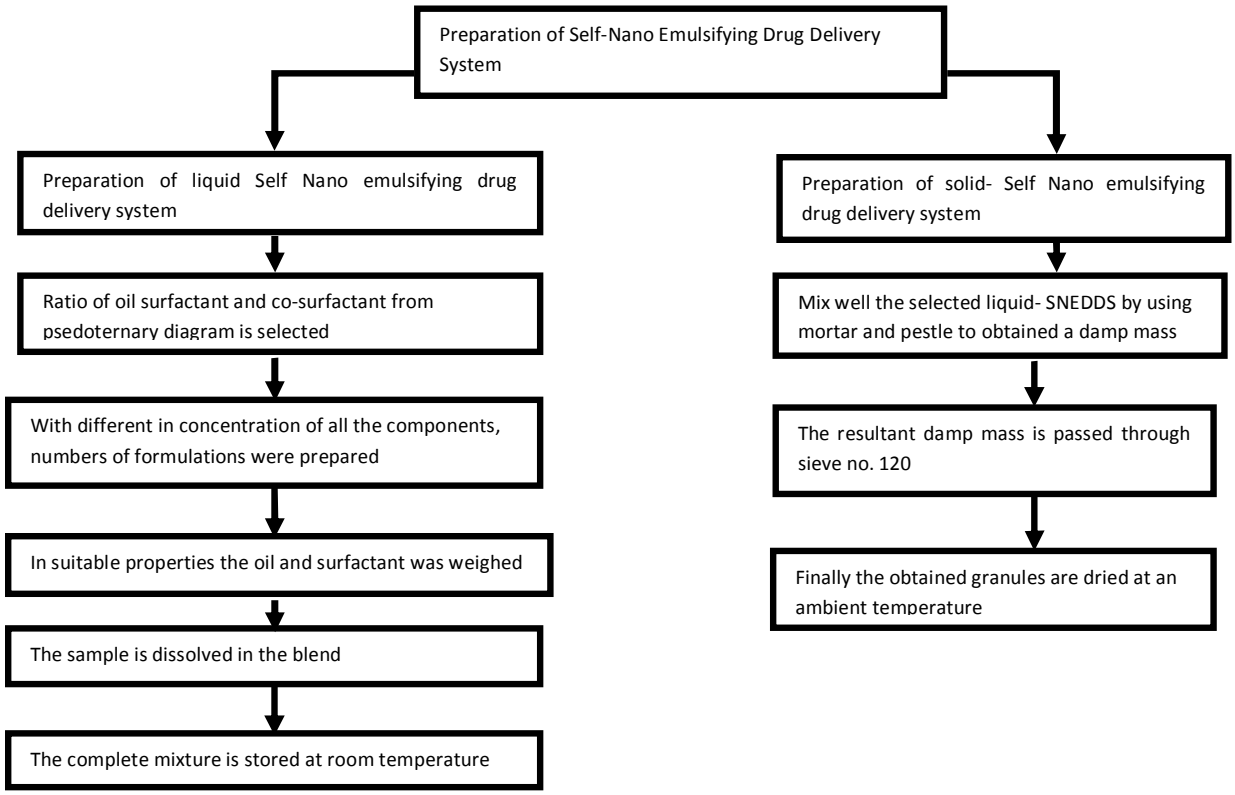

Fig. 1. Flowchart for the SNEDDS procedure.

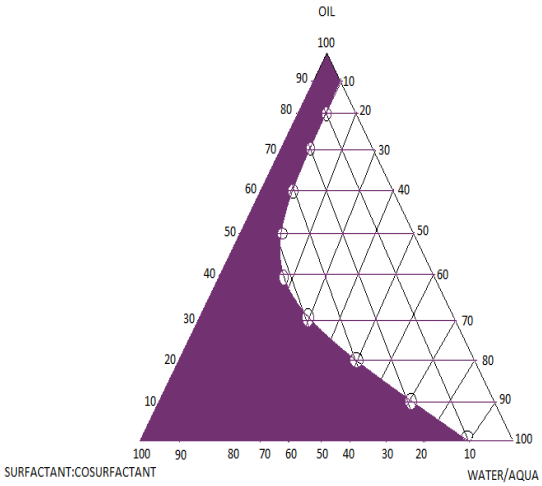

Fig. 2. Pseudoternary Phase Diagram

CONCLUSION

The novel and advanced approach nowadays is the nanotechnology in which one of the unique approach is the formulation of the Nano emulsions such as SNEDDS of less aqueous soluble drug so as to increase its rate of solubility, bioavailability and absorption, hence helps in improving both dissolution rate and rate of absorption of the drug molecule and development of the less soluble drugs in all aspects. SNEDDS is one of the isotropic mixture of the components such as oil, Smix, solvents/co-solvents and hence it is introduced into aqueous medium, gets self-emulsified instinctively to produce fine Nanoemulsion/self-emulsified Nano emulsion such as o/w, w/o and multi emulsions using various techniques and some of them can be obtained on gentle agitation. The formulation of the SNEDDS can also be formulated in oral route of the BCS class IV drugs/ lipophilic drugs and here there is the use of the herbal drugs which is formulated into SNEDDS where the oil of the herbals is extracted from the crude drug and then it is used for the preparation. The oils that are used can be either essential oils or fixed oils which are based on the crude material and some of the oils have less solubility,oral bioavailability and absorption rate, hence by formulating them into SNEDDS may help to overcome these drawbacks. The prolong release is important hence polymers are incorporated in the composition. By applying the nanotechnology in many formulations as well as in herbal preparations might help in improving their solubility bioavailability as well as the rate of absorption by formulating them into Nano sized formulations.

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