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Self-Nano Emulsifying Drug-Delivery Systems: From the Development to The Current Applications and Update of the Biopharmaceutical Aspect †

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Abstract: Almost one third of newly discovered drug molecules show incompetent water solubility and therefore low-set oral bioavailability. Different lipid-based formulations have been investigated in the past few decades to improve the oral delivery of such compounds. Self-Nano emulsifying drug delivery systems (SNEDDS) are one of the effloresc ing strategies developed to concentrate on the issues associated with their oral delivery. Self-Nano emulsifying drug delivery systems (SNEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to enhance the oral absorption of highly lipophilic drug compounds. The efficaciousness of oral absorption of said drug from such type of formulation constrained by many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which are importance determine the self-emulsification ability. With the growing engrossment in this field, there is an increasing Prerequisite for selection of excipients guidelines to achieve efficacious and safe delivery system with enhance bioavailability. The goal of this review is to extant mechanism of self-emulsification, composition, role of various excipients, formulation approaches, different techniques, evaluation parameters, factors affecting SNEDDS, Biopharmaceutical aspects and future perspective. The present review gives vision of SNEDDS for the oral administration of both lipophilic and hydrophilic compounds.

Keywords: Oral bioavailability; Self-Nano Emulsifying Drug Delivery Systems (SNEDDS), lipid formulation classification system (LFCS).

1. Introduction

The oral administration route is the promoted perspective of drug administration due to its safety, patient compliance, and capacity for self-administration. In addition to being the most acceptable route of administration, oral delivery has been restricted to the multitudinous barriers present at the gastro-intestinal (GI) tract. The solubilization of the drug within the GI tract is essential for the drug absorption, as inadequate drug dissolution may finally conduct to incomplete absorption, low bio-availability, and high variability following oral administration [1]. Various endeavor is ongoing to boost the oral bioavailability of lipophilic drugs in order to increase their clinical effectiveness. Different lipid-based formulations were scrutinized in the past few decades to upgrade the oral delivery of lipophilic drugs. In recent years, the prominent approach is their incorporation into self-emulsifying drug delivery systems (SEDDS) with particular attention on self-nano emulsifying drug delivery systems (SNEDDS). SNEDDS are described as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or, alternatively, one or more hydrophilic solvents and co-solvents/ surfactants [2-3]. When SNEDDS formulation is delivered, in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/nano) so called as in situ emulsification or self-emulsification which extraneous leads to solubilization of drug that can subsequently be absorbed by lymphatic pathways, hepatic first-pass effect. SNEDDS are nano emulsions formed by heterogeneous dispersions of two immiscible liquids (oil-in-water [O/W]

or water-in-oil [W/O]) having a mean droplet size in the nanometric scale (typically 20- 200 nm), nevertheless. of method of preparation. This is extremely important for drugs for enhancing the solubility.

The Self-Nano Emulsifying Drug Delivery System is also known as Nano emulsion, Mini emulsion, ultrafine emulsion, Submicron emulsion. This bioavailability complementing property has been associated with a number of in-vivo properties of the lipid formulations including: (a)Formation of fine dispersions and micellar suspensions to restrict precipitation and re-crystallization of the drug compound. (b)Ability of certain lipid compounds and their metabolites to hustle changes in the gastrointestinal fluid to favour improved drug absorption. (c) Suppression of cellular efflux mechanisms, which keep drugs out of circulation. Certain lipid excipients are affiliated with selective drug uptake into the lymphatic transport system, consequently reducing the effect of first-pass drug metabolism.

2.Composition of SNEDDS and their role in formulation performance [4]: To entitle distinction among various lipid-based carriers, Pouton et al. [1] established the lipid formulation classification system (LFCS). According to LFCS, SNEDDSs pertain to class III compositions, which are composed of oils and water-soluble surface-active agents (surfactants and cosurfactants) and may also comprehend cosolvents. Fortuitous formulation of a SNEDDS requires consideration when selecting formulation ingredients.

2.1. Active Pharmaceutical Ingredient (API): As, SNEDDS are used to increasement the solubility of poor water-soluble drugs, BCS class II drugs are favored. Drugs which are administered at very high dose are not suitable for except they exhibit tremendously good solubility in at least one of the components of SNEDDS, preferably lipophilic phase. The drugs which disclose high melting point and limited solubility in water and lipids typically with log P values of close to 2 are most demanding to deliver by SNEDDS.

2.2 Excipients used in SEDDS Considering, pharmaceutical appropriateness and the toxicity issues the selection of excipients is really crucial. So, there is a great constraint as to which excipients should be used. The self-emulsification process is distinct to the concentration and nature of the oil/surfactant ratio, surfactant/co-surfactant ratio and the temperature at which self-emulsification occurs. So, this entire factor must be scrutinized during selection of excipients in SNEDDS.

2.2.1. Oil: Oils can solubilize the required dose of the lipophilic drug and hasten self- emulsification and also, they can improvement the fraction of lipophilic drug transferred via the intestinal lymphatic system, thereby promoting absorption from the GI tract hanging on the molecular nature of the triglyceride. Natural edible oils remain the relevant and thrust oil ingredients, but they exhibit relatively low drug-loading capacity and poor emulsification efficiency. Modified medium-chain triglycerides (MCTs) and long-chain triglycerides (LCTs) are mostly committed to enhance the drug solubility in the formulation. MCTs are predominantly composed of triglycerides with lipid chain lengths ranged from lipid chain lengths ranging from C8 to C10 while LCTs consist of TG with lipid chain lengths surpassing C10 MCT are more soluble and have raised mobility in the lipid/water interfaces than LCT associated with accelerated hydrolysis of MCT. MCTs are recommended because of their stronger solubilizing ability and self-emulsification capacity as well as increase the drug transport straight through the portal vein, but they have a defined capacity to strengthen the lymphatic transport of the drugs. On the other hand, LCTs are bypassing the hepatic first-pass metabolism and build up the transport of drugs through lymph vessel. Thus, a mixture of MCTs and LCTs can be attentiveness, to meet optimum properties and enhance pharmacokinetics.

2.2.2. Surfactant: The surfactant is the most crucial component of SNEDDS formulation for improving the solubility of poorly water-soluble drugs. Surfactant reveal the essential emulsifying characteristics to the SNEDDS. Surfactants of natural origin are favored because they are safer than the synthetic surfactant. The selection of a particular surfactant for formulation relies upon its HLB value and safety issue. The most conventional are the non-ionic surfactants with a relatively high HLB. The non-ionic surfactants are nontoxic as compared to the ionic ones. The most typically used non-ionic surfactant includes Tween 80) and Pluronic F127. Usually, a stable SNEDDS formulation requisite high concentration of surfactant (30 to 60%). The droplet size of the emulsion is conversely affected by the concentration of the surfactant. Still high concentration of surfactant may cause irritation to the gastric mucosa. On the account of the safety is major considerable parameter for choosing of Surfactant molecule.

2.2.3. Cosurfactant: Co-surfactant is indistinguishable function to surfactant unit. Co-surfactant was added along with surfactant unit to enhance the ability of Surfactant to boosting water solubility of poorly water-

soluble drug. The co-surfactant is able to obviate the Interfacial Fluidity. The co-surfactant molecule is come into contact with surfactant, oil and water it can distinguished by Monomolecular Layer of surfactant molecule and counteract interfacial tension between oil and water interface. The newer cosolvents like Transcutol™ and Glycofurol™ have abundant advantages over the traditional ones, including superior stability and less volatility

2.2.4. Viscosity Enhancers: The viscosity of the emulsions can be recasting by the use of additional material such as acetyl alcohol, tragacanth, beeswax and stearic acids etc.

2.2.5. Polymers: Polymer matrix (inert) present in 5 to 40 % w/w, which is not ionizable at physiological pH are acquiesce to form matrix. Examples are hydroxyl propyl methyl cellulose, ethyl cellulose, etc.

2.2.6. Antioxidant Agents: Lipophilic antioxidants (e.g., α tocopherol, propyl gallate, ascorbic palmitate) sustain the oily content of SNEDDS formulations.

3. Mechanism of Self-emulsification [5]: According to Reiss, the energy needed to increase the surface area of the dispersion endure less importance as compared to the entropy change that satisfy dispersion. In case with the conventional emulsion formulation, the free energy is required to fabricate a new surface between the oil and water phases. The net free energy (ΔG) change of the system is deliberated by following equation,

$$\Delta G = \Sigma N \pi r^2 \sigma$$

Where, N = Number of droplets

r = Radius

σ = Interfacial energy.

The depletion in the interfacial tension occurs as the two phases of the emulsion separate out additionally minimize the free energy of the system(s). The main function of emulsifier is to lower the interfacial tension and thus shield of coalescence. The readily penetration of water into several liquid crystals or gel phases formed on the surface of the droplet hasten emulsification process.

4. Factors affecting SNEDDS performance [6] Recognizable and inconstant factors that may affect the performance of SNEDDS may include but not limited to the following:

4.1. Nature and Dose of the Drug: Generally, drug molecules requisition larger effective therapeutic concentrations do not present as prospective candidates for SNEDDS development unless they exhibit tremendously good solubility in at least one of the components of SNEDDS, preferably lipophilic phase. The drugs which disclosed limited solubility in water and lipids typically with log p values of approximately 2 are most difficult to hand over by SNEDDS. The ability of SNEDDS to maintain the drug in solubilized greatly altered by the solubility of the drug in oil phase.

4.2 Concentration of Surfactant or Co- surfactant: If surfactant or co-surfactant is bringing on the greater extent in drug solubilization then there could be a possibility of precipitation, as dilution of SNEDDS will effectuate lowering of solvent capacity of the surfactant or co-surfactant.

4.3 Polarity status of lipid phase: The nature and eminence of the polarity of the oil/lipid phase is one of the dominant factors governing the performance of drug loaded lipid-based formulations. Substantially, the type of forces existing in the system as well as the affection of drug molecules for oil or water phase is highly dependent on the polarity factor. The polarity of the lipid phase is directly commanding the drug release from the Nano emulsions and it is supervised by the HLB, the chain length and degree of unsaturation of the fatty acid and molecular weight of micronized drug. It was interposed that the formulation that possessed the highest polarity was associated with the highest drug release rate.

5. **Preparation of SNEDDS:** The preparation assumes the addition of drug to the mixture of oil, surfactant, and cosurfactant and then it should be exposed to vortexing. In some cases, drug is dissolved in any one of the excipients and the left-over excipients are added to the drug solution. Then, the solution should be properly mixed and tested for the indication of turbidity. After equilibration at ambient temperature for 48 hours, the solution should be heated for the formation of clear solution, if required. Fortuitous the final volume, the formulation should be stored in capsules of suitable size.

6. Optimization of SNEDDS Formulations [7]: After selecting prospective components of SNEDDS, optimization studies are carried out to secure the optimum amounts of oily phase, surfactants, and cosolvents that surrender spontaneous Nano emulsion. Ternary phase diagrams are extensively used to identify the emulsification area for selected components. In ternary diagrams, the ratio of one component varies while the concentrations of the other two are confirmed. The emulsification area is point out visually or by measuring the particle size of the

emulsion/nano emulsion emerging after aqueous dispersion. All the SNEDDS compositions from the emulsification area return spontaneous Nano emulsions, with globule sizes less than 200 nm after aqueous dispersion. Furthermore, ternary phase diagram SNEDDS optimization can also be conducted with different stastical experimental design, such as Box–Behnken design, Central composite design, Simplex lattice design, Full-factorial design, and D-optimal design. Advantage of these statistical experimental designs is that they can reduce expenditure in terms of time, resources, and developmental efforts.

7. Characterization of SNEDDS [8]: It is crucial to evaluate the final SNEDDS for several parameters. The general techniques and methods that have been engaged for SNEDDS characterization are followings.

7.1 Thermodynamic Stability Studies: This study is extensive for product performance as it can be negative impact on precipitation of the drug in excipient matrix.Poor physical stability of formulation can induce phase separation of excipients which affects bioavailability as well as therapeutic efficacy.

7.1.1. Heating Cooling Cycle: Six cycles between refrigerator temperature 4^{0}C and 45^{0}C with storage at each temperature of not less than 48 h will be studied. Those formulations, which are enduring at these temperatures are then subjected to centrifugation test.

7.1.2. Centrifugation: Formulations get ahead the heating cooling cycle are centrifuged at 3500 rpm for 30 min. Those formulations that do not show any phase separation are collected for the freeze thaw stress test.

7.1.3. Freeze Thaw Stress Cycle: Three freeze thaw cycles b/w -21 °C and 25 °C with storage at each temperature for not less than those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then run through dispersibility test for assessment of self-emulsification efficiency.

7.2. Dispersibility Test: The dispersibility test of SNEDDS is accomplish to assess its capability to disperse into emulsion and categorize the size of resulting globules. It is performed 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 ^{o}C and the paddle is rotated at 50 rpm. On titration with water the SNEDDS formulation proliferate (within 1 min) Nano emulsion, having a clear or bluish appearance indicates the formation of Nano emulsion.

7.3. Morphology and Particle Size: The morphology of the Nano emulsion droplets can be set on by scanning electron microscopy (SEM) and transmission electron microscopy (TEM)). Recently, cryo-SEM and cryo-TEM have been flourished to study the real morphological information of Nanoparticles. The literature relay that smaller particle size has a positive effect on the oral bio-availability of a drug encapsulated into SNEDDS. Small mean droplet size contributes large interfacial area for drug absorption and confirm the kinetic stability of the resulting emulsion.

7.4. Drug Content: Drug from pre-weighed SNEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is explored by suitable analytical method.

7.5. Zeta Potential*:* The zeta potential imparts information about the colloidal stability. It is assessed by measuring the electrophoretic mobility of the droplets. The presence of a high zeta potential value (±40 mV) express repulsive electrostatic forces, which reduces the possibility of particle aggregation.

7.6. Viscosity Measurement*:* The SNEDDS system can be distributed in soft gelatin capsules, where, it should have significant flow properties for processing. Low-viscosity formulations create leakage concerns, whereas overly viscous SNEDDSs are hardly filled into capsules due to flowability problems. The rheological properties of formulation were regulated by rotational viscometers,digital instruments coupled with either cup and bob or coaxial measuring device.

7.7. Refractive Index (R.I.) and Percent Transmittance: Refractive Index and percent transmittance are determined to examine the transparency of formulation. Refractive Index of the formulation is measured by refractometer by positioning drop of solution on slide and then comparing with water. The percent transmittance of the formulation is measured at a particular wavelength using UV spectrophotometer on account of distilled water as blank.

7.8. Robustness to Dilution: Emulsions upon dilution with various dissolution media nonexistent any phase separations or precipitation of drug regardless of 12 hr. of storage, such formulation is considered as robust to dilution.

7.9. Cloud Point Measurement: Cloud point is determined as the temperature over and above the emulsion clarity turns into cloudiness which is accredited to the dehydration of polyethylene oxide moiety of non-ionic surfactants. Cloud point could be measured after 100-fold dilution of the preconcentrate with distilled water which is then

accommodated in a water bath with gradual increase in temperature. Additionally,spectrophotometric analyses are carried out to determine the transmittance percentage of the sample. The increase in transmittance can be used to observe the self-emulsification rate, and the final transmittance percentage is usually corresponded with the nanoparticle droplet size.

7.10. *In-vitro* Diffusion Study: This study is done to determine attitude of formulation using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialyzing medium. One end of the dialysis membrane is tied with a thread and 1ml of the SNEDDS formulation accompanying 0.5 ml of dialyzing medium are filled in the membrane. While, the other end of membrane is tied with thread and allowed to rotate in dialyzing medium at 100 rpm utilizing magnetic stirrer or dissolution apparatus. Samples are withdrawn at different time intervals and investigated.

7.11. *In-vitro* Dissolution Technique: The *invitro* dissolution studies are executed to assess drug release from oil phase into aqueous phase by USP type 2 dissolution apparatus employing 500 ml of simulated gastric fluid containing 0.5 % w/v of SLS at 50 rpm and maintaining the temperature at 37 ± 0.5 ºC. Aliquots of samples are withdrawn at different time intervals and investigated by using UV spectrophotometer or any other suitable approaches.

8. Solid SNEDDS [9]: Even though the benefits provided by liquid SNEDDSs, disadvantage such as drug/components precipitation when stored, interactions between the filling and the capsule shell, and formulation stability during storage are regular issues faced by them. The main strategy applied to conquer these challenges is to transform liquid SNEDDS into solid dosage SNEDDS formulations. It is presumed that the conversion of liquid SNEDDS to solid SNEDDS provides relatively lower production cost, better formulation stability, ease of handing, precise dosing, and, subsequently, better patient compliance. Generally, the techniques engaged to develop solid SNEDDSs cover adsorption onto inert carriers, spray drying, melt granulation and extrusion-spheronization.

9.BioPharmaceutical Aspects for Formulation Design [8]: SNEDDS have a prospective to increase oral bioavailability by collaborative mechanisms. SNEDDS present drugs in a small droplet size and well-proportioned distribution and improve the dissolution and permeability. Again, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SNEDDS protect drugs against hydrolysis by enzymes in the GI tract and reduce the pre -systemic clearance in the GI mucosa and hepatic first-pass metabolism. Following points should be check out for successful formulation of SNEDDS:

9.1. The capability of the formulation is case specific in most occasion thus, composition of the formulation should be resolute very carefully.

9.2. Considering relatively high concentration of surfactants is generally employed in the SNEDDS formulation, toxicity of the surfactant being used should be count on. Realistically a compromise must be accomplished between the toxicity and self-emulsification ability of the surfactant that is considered for use.

9.3. A systematic explanation of the rationale may be attained by a pre selecting excipients for their fatty acid make up, melt characteristics, HLB or emulsification properties, potential effect on enterocytes-based drug transport and disposition and overall digestibility.

9.4. Regulating binary screening with the preselected excipients for drug solubility, compatibility, stability, and dissolution/dispersion properties to recognize one or more suitable systems for further studies.

9.5. Distinguishing the formulation techniques appropriate for the dosage form considered as well as confirming the *in vivo* performance of the chosen formulation system in appropriate animal models.

9.6. Optimizing the compositions per individual physicochemical properties and absorption processes of a drug.

9.7 Exhaustive understanding of the spontaneous Nano emulsification process, physicochemical and biological properties of the components used for the construction of SNEDDS are important for successful formulation of SNEDDS.

10. Improvement of oral absorption by SNEDDS [8]: Many studies accomplished in animals for the assessment of the oral bioavailability of hydrophobic drugs developed in SNEDDS. Pharmacokinetics studies play a vital role in forecasting the oral bio-availability in humans during drug development. There are hundreds of published articles on pharmacokinetics studies with SNEDDS formulations reveal raised bio-availability in animals such as rats, dogs, or rabbits as well as in human. Examples of bioavailability intensification of SNEDDS formulations and some of the marketed formulations are mentioned in Table 1 and 2 respectively.

Table 1. Pharmacokinetics data appear on enhanced bio-availability from SNEDDS in human subjects.

Drug	Components	In Vivo Observation
Vitamin E	Palm oil, Tween® 80, Span® 80	3-fold higher oral bio-availability from SNEDDS
Cyclosporin	Corn oil glycerides, Cremophor® RH40, PG DL-α-tocopherol and ethanol	AUC_{0-t} and Cmax increased 1.18 and 1.17-fold, respectively from SNEDDS.
Tocotrienols	Tocomin, Soybean oil Tween® 80 Labrasol®	2 to 3-fold higher oral bio-availability from SNEDDS.
Saquinavir (Fortovase®)	Medium-chain mono- and di Glycerides	Increased oral bio-availability up to 331% from Fortovase® compared to Invirase®.
Simvastatin	Labrafil®, Tween® 80, Transcutol HP	1.55 and 1.5 increased in Cmax and AUC_{0-t}, respectively from SNEDDS
Vitamin K	Vitamin K, Labrasol®, Transcutol HP	Enhancement in vitamin K relative bio-availability from SNEDDS

Table 2. Non-exhaustive list of merchandised SNEDDS for oral administration.

Drug Name	Trade Name	Company	Dosage Form
Tretinoin	Vesanoid®	Roche	Soft Gelatin capsules(10mg)
Tipranavir	Aptivus®	Boehringer Ingelheim	Soft Gelatin capsules (250 mg)
Cyclosporine A	Gengraf®	Abbott	Hard Gelatin capsules (25, 100mg)
	Sandimmune®	Novartis	Soft Gelatin capsules (25,50,100 mg)
Isotretinoin	Accutane®	Roche	Soft Gelatin capsules (10,20,40mg)
Lopinavir and Ritonavir	Kaletra®	Abbott	Soft Gelatin capsules Lopinavir 133.33mg and Ritonavir 33.3 mg

10.Future Perspective and conclusion: The utilization of lipid-based formulations in general and SNEDDS in particular shows great prospective in upgrade aqueous solubility, stability, oral absorption and diminish inter/intra-patient dose variability. SNEDDS ameliorate the absorption of drugs by several pathways. Composition of the SNEDDS should be determined very deliberately. Considering a relatively high concentration of surfactants is generally employed in the formulation, toxicity of the surfactant being used should be taken into consideration. SNEDDS are prepared generally in liquid dosage forms but solid SNEDDS are favored due to ease in handling, transportation and better stability. Also, it escapes GI irritation and controlled and sustained release of drug is achievable. Non appearance of suitable *in vitro* models explaining the state whether dissolved or not in G.I.T for evaluation of SNEDDS are major hurdles. Further, with solid SNEDDS, compatibility and interactionstudies between the excipients such as adsorbent, capsule shell and formulation components can be implement in order to effectively tackle its potential for the service of mankind. So, we can conclude that SNEDDS appear to be as unique and industrially longevity approach with future development.

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