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A CONCISE REVIEW ON SELF NANOEMULSIFYING DRUG DELIVERY SYSTEM: A POTENTIAL TOOL TO INCREASE DRUG BIOAVAILABILITY

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ABSTRACT: Oral route is the easiest and most convenient route for drug administration more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Self-nano-emulsifying drug-delivery systems (SNEDDSs) are one of the emerging strategies developed to tackle the issues associated with their oral delivery. SNEDDSs are composed of an oil phase, surfactant, and cosurfactant or cosolvent. SNEDDSs characteristics, their ability to dissolve a drug, and *in-vivo* considerations are determinant factors in the choice of SNEDDSs excipients. SNEDDS is a proven method for enhancing solubility and bioavailability of lipophilic compounds. Considering the ease of large-scale production and the robustness of SNEDDS, several formulations techniques are commercially available. The review provides exhaustive insight about the potential of SNEDDS in improving bioavailability of poorly soluble drugs.

INTRODUCTION: Self emulsifying drug delivery systems (SEDDS) also called as self emulsifying oil formulation are mixtures of oils and surfactants, ideally isotropic, and sometimes Containingco-solvents, which emulsify spontaneously to produce fine oil in water emulsion when introduced into aqueous phase under gentle agitation. Self nanoemulsifying (SNEDDS), self micro emulsifying (SMEDDS) and self emulsifying drug delivery system are the systems which improve the oral bioavailability of poorly water-soluble drugs.

Self Emulsifying Drug Delivery System: SEDDS are defined as isotropic mixtures of one or more hydrophilic solvents and co-solvents/surfactants that have a unique ability of forming fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids. SEDDS are used to solve low bioavailability issues of poorly soluble & highly permeable compounds.

When SEDDS formulation is released in the lumen of the gastrointestinal tract, they come in contact with GI fluid and form a fine emulsion (micro/ nano) so called as in-situ emulsification or self emulsification which further leads to solubilization of drug that can subsequently be absorbed by lymphatic pathways, bypassing the hepatic first-pass effect.

This bioavailability enhancing property has been associated with a number of *in-vivo* properties of the lipid formulations.

Self Emulsifying Drug Delivery System is divided into two types:

1. Self Micro Emulsifying Drug Delivery System.
2. Self Nano Emulsifying Drug Delivery System.

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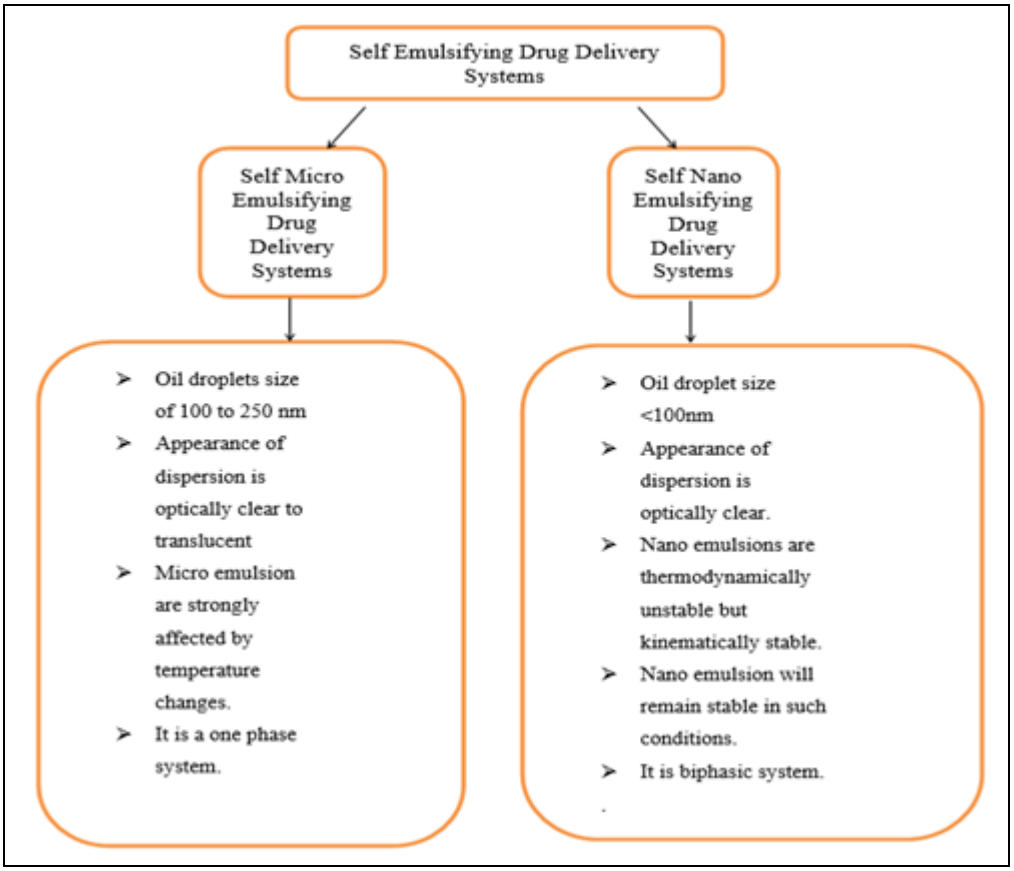

Advantages of SEDDS [1, 2]:

- ❖ Quick Onset of Action Reduction in the Drug Dose Ease of Manufacture & amp; Scale-up.
- ❖ Improvement in oral bioavailability.
- ❖ Inter-subject and Intra-subject variability and food effects.
- ❖ Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
- ❖ No influence of lipid digestion process.

Disadvantages of SEDDS [2]:

- ➢ Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
- ➢ This *in-vitro* model needs further development and validation before its strength can be evaluated.
- ➢ Further development will be based on *in-vitro*, *in-vivo* correlations and therefore different prototype lipid-based formulations needs to be developed and tested *in-vivo* in a suitable animal model.
- ➢ The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) within GIT.

Nanoparticles: Nanoparticles are defined as particulate dispersions or solid particles with a size in the range of 10-1000nm.The major role in designing nanoparticles as delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve site specific action of drug at therapeutically optimum rate and dose regimen.

Advantages of Nanoparticles:

1. Particle size and surface characteristics of Nanoparticles can be easily manipulated to achieve both passive and active drug targeting after parenteral administration.
2. Site-specific targeting can be achieved by attaching targeting ligands to the surface of particles or use of magnetic guidance.

3. The system can be used for various routed of administration like oral, nasal, parenteral, intra ocular, *etc*.

Self nano-emulsifying Drug Delivery System: Self-nano emulsifying drug delivery system (SNEDDS) are isotropic mixtures of oil, surfactant, co-surfactant and drug that form fine oil-in- water nanoemulsion when introduced into aqueous phases under gentle agitation. SNEDDS spread readily in the gastrointestinal tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for self-emulsification [3].

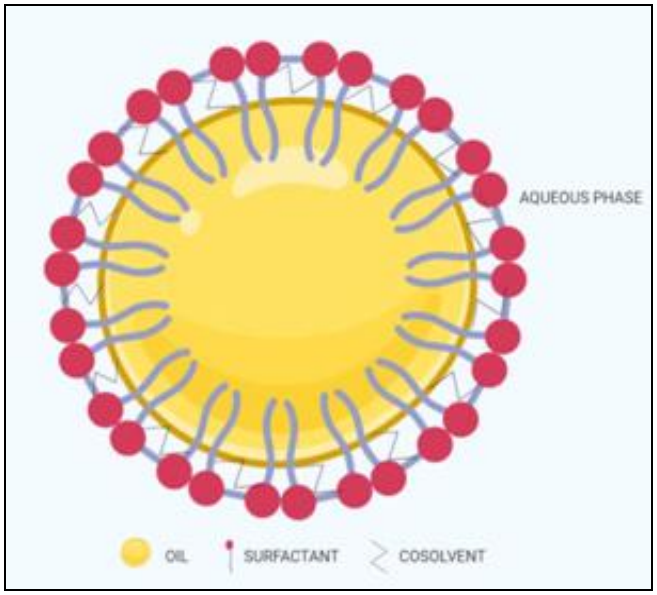

FIG. 1: TYPICAL STRUCTURE OF SNEDDS

Advantages of SNEDDS:

1. It provides protection to sensitive drug substances.
2. It facilitates selective targeting of drug(s) toward specific absorption window in GIT.
3. It enhances oral bioavailability enabling reduction in dose.
4. It provides high drug payloads.
5. It can be easily stored since it belongs to a thermodynamics stable system.
6. Fine oil droplets would pass rapidly and promote wide distribution of the drug throughout the GIT, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
7. As compared with oily solutions they provide a large interfacial area for partitioning of the drug between oil and water [4-6].

Disadvantages of SNEDDS:

- ✓ Lack of good predicative in vitro models for assessment of the formulations because traditional dissolution methods do not work, also these formulations potentially are dependent on digestion prior to release of the drug.
- ✓ To mimic this, an *in-vitro* model simulating the digestive processes of the duodenum has been developed.
- ✓ Need of different prototype lipid based formulations to be developed and tested **in-vivo** in a suitable animal model [7, 8].

Factors affecting SNEDDS:

- ❖ Drugs which are administered at very high dose are not suitable for SNEDDS, unless they exhibit extremely good solubility in at least one of the components of SNEDDS, preferably lipophillic phase. The drugs that exhibit limited solubility in water and lipids are most difficult to deliver by SNEDDS.
- ❖ The ability of SNEDDS to maintain the drug in solubilized form is greatly influenced by the solubility of the drug in oily phase. If the surfactant or co- surfactant is contributing to a greater extent for drug solubilization, then there could be a risk of precipitation, as dilution of SNEDDS will lead to lowering of solvent capacity of surfactant or co-surfactant [9].

Excipients:

Oil: Generally selection oil used in formulation of SNEDDS is based on its solubility parameter, HLB (Hydrophilic Lipophilic balance) value, degree of esterification, melt aspect and also some physical characterstic [17]. Oils are triglyceride lipidemic formulation. There are some vegetative oil formulation like hydrogenated castor oil, hydrogenated soybean oil [10].

TABLE 1: COMMONLY USED OILY PHASE

General class	Examples	Commercial name
Medium chain triglyceride	Triglycerides of capric/caprylic acids	Miglyol 810, 812, Labrafa CcCrodamol GTCC, Captex 300, 355
Medium-chain mono and di-glycerides	Mono and di-glycerides of capric/caprylic acids	Capmul MCM, Imwitor 742, Akoline MCM
Long-chain monoglycerides	Glyceryl monooleate	Peceol, Capmul-GMO
Propylene fatty acid esters	PGmonoc caprylate	Capryol 90, Capmul PG-8, Sefsol 218

Surfactant: The selection of surfactant is based on the required HLB value to form o/w Nanoemulsion is greater than [10]. The right blend of low and high HLB surfactants leads to the formation of a stable Nano emulsion upon dilution with water also able to lower interfacial tension to a very small value to aid dispersion process during the preparation of the Nano emulsion which Provide a flexible film that can readily deform around droplets and be of the appropriate lipophilic character to provide the correct curvature at the interfacial region for the desired Nanoemulsion type [11].

TABLE 2: COMMONLY USED SURFACTANT

General class	Examples	Commercial name
Polysorbates	Polyoxy ethylene-20-sorbitan monoleate	Tween 80, Crillet 4
Sorbitan esters	Sorbitan monooleate	Span 80, Crill
Polyoxyethylene castor oil	Polyoxyethylene-35-castoroil	Cremphor EL. Etocas 5
Polyoxy ethylene hydrogenated castor oil	Polyoxyethylene-40-hydrogenated castoroil	Cremphor RH60, HCO-60
Polyoxyethylene stearate	Polyethylene glycol-660-12-hydroxystearate	Solutol HS15
Polyoxyethylene-vitaminE	Tocopheryl Polyethyleneglycol 1000-succinate	Vitamin ETPGS
Sucrose esters	Sucroselaurate	----------
Polyglycolyzed glycerides	Linoleoyl macrogolglycerides	Labrafil 2125CS

Co-Surfactant: Co-surfactants like medium chain alcohols (5–8 carbon units), is weakly amphiphilic molecules, assumed to concentrate in the surfactant layer of the aggregates formed by the primary surfactant. Due to their weak amphiphilic character, co-surfactants alone do not form aggregates, but they strongly support aggregation of the primary surfactant. In the absence of co-surfactant, a highly rigid film is formed by a surfactant and thus produces nano emulsion over only a very limited range of concentration.

The presence of co-surfactants allows the interfacial film sufficient flexibility to take up different curvatures required to form Nano emulsion over a wide range of composition. Mixing long and short-chain surfactants leads to more flexible interfaces compared to usage of surfactants with a chain length intermediate between the long and the short one [12].

Methods: As stated in the preceding section, NEs are very small in size, and by using equipment with high pressure, the tiny particles can be obtained. Currently, high and low energy emulsification methods can be utilized to fabricate NEs. Depending on the methods exploited, many types of emulsion systems comprising functional compounds have been prepared and investigated.

High Energy Emulsification Methods: Different mechanical methods such as high- pressure homogenization (HPH) or microfluidizers and ultrasonication have been applied in high energy emulsification to form intensive disruptive forces like collision, compression, and cavitation, which allows one phase to be dispersed into another as tiny droplets [13].

In high energy emulsification methods, the emulsion is produced by using mechanical equipment. Despite the efficacy of these high energy methods in decreasing the size of particles, they are very unlikely for thermolabile drugs and macromolecules such as proteins, enzymes, retinoids, peptides, and nucleic acids [14]. This is because high energy methods deal with high temperature and pressure, which could potentially damage thermolabile or sensitive drugs as well as proteins.

High-Pressure Homogenization: All in all, conventional high-pressure homogenizers employ pressures between 50 and 100 MPa.

Nevertheless, with new technologies, an instrument utilizing pressures as high as 350 MPa has been developed recently [15]. In HPH, a small gap usually with a gap height around 1 to 10 nm causes the sudden pressure drop across HPH to reach a few thousand bars; the different phases composed of oil, water, and surfactant are forced into droplets and experience extreme shear and elongation leading the droplets to be disrupted into finer droplets. The mixture is typically passed many times through the homogenizer until the droplet size is approximately constant [16-18]. Due to many different factors, for example, turbulence, and elongational and shear stress as well as cavitation, the fluid-dynamic stresses in HPH become higher. In the homogenization chamber, three flow patterns of disruption units can befound.

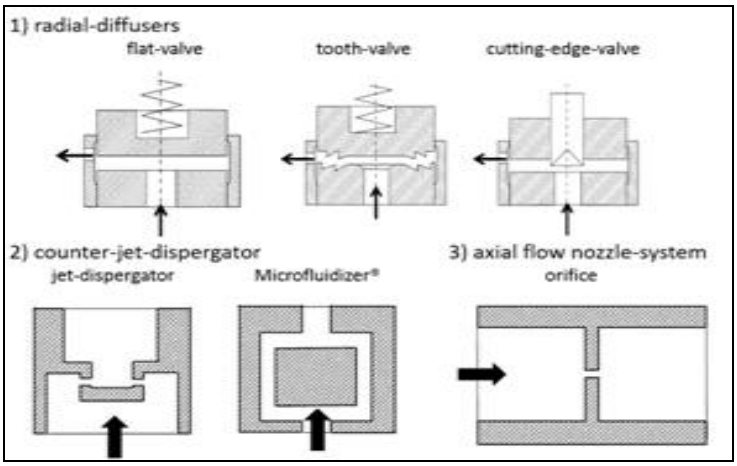

FIG. 2: SCHEMATIC DIAGRAM OF HIGH PRESSURE HOMOGENIZER

Radial diffusers are comprised of an axially mobile seat that allows for variation in the flow rate by changing the slit width [17]. The counter-jet dispergator includes a collision area of two or more opposed jets of the emulsion. There are no movable parts for counter-jet dispergators or the axial flow-nozzle systems, which makes them suitable for very high pressures. Nozzle aggregates can be distinct by their axial flow direction. The most important advantages of HPH for industrial production is that it is scalable, easy to operate, efficient, and has high reproducibility [18]. There are two methods that can be used in HPH, which are the hot or cold HPH technique. Both techniques have their own advantages, but the cold HPH technique is used for extremely temperature-sensitive compounds [19]. In both techniques, the active compound is dissolved or dispersed in the melted lipid phase, but in the hot HPH technique, the mixture is dispersed into a hot surfactant solution above the melting point by high-speed stirring, whereas in the cold HPH technique, the combination of the active compound and lipid phase is cooled down, ground, and then dissolved into a cold surfactant solution so that a cold pre-suspension of micronized phase is formed [20].

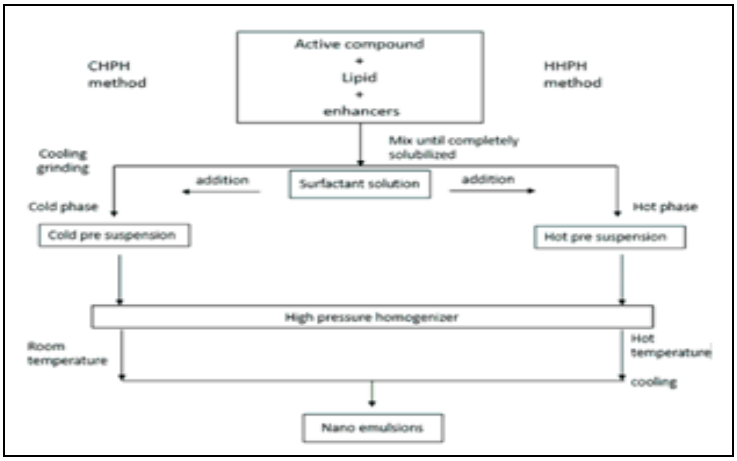

FIG. 3: SUMMARY OF NE PRODUCTION PROCESS USING COLD AND HOT HPH

Advantages:

1. Low risk of product contamination.
2. Allows aseptic production of nano suspensions for parentral administration
3. Particle size may reduced up to 1nm.

Microfluidization: The microfluidization technique is a technology that utilizes a device called a 'microfluidizer', which also uses high pressure. This method forces the product through the interaction chamber with small channels called microchannels inside using a high- pressure positive displacement pump (500–200 psi). Then, the process follows on through the microchannels to an impingement area that forms tiny particles of the submicron range. The aqueous phase and oily phase are mixed and processed in an inline homogenizer to obtain coarse emulsion. Finally, to obtain stable, small-sized NEs, the coarse emulsion is further processed in the microfluidizer. This technique does not require pre- emulsification as the dispersed phase is injected directly into the continuous phase through micro channels and is known as the 'direct' emulsification technique. This is considered to be a big advantage over the HPH method [21]. From the mechanical point of view, the microfluidizer is a high- velocity version of a static mixer that has no moving parts [22]. The advantage of this method is that it can be applied at both a laboratory and industrial scale.

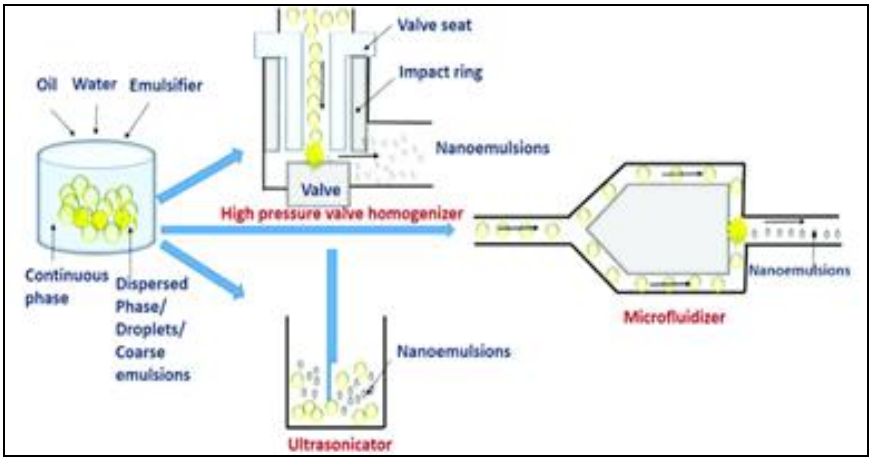

FIG. 4: SCHEMATIC IMAGE OF A HIGH PRESSURE MICROFLUIDIZER

Advantages:

1. Simple and rapid.
2. Electric fields are unnecessary.
3. Reduced size polydispersity.

Ultrasonic Emulsification: The ultrasonic emulsification method is proficient in minimizing the size of NEs. In ultrasonic emulsification, sonotrodes called a sonicator probe provide the energy to break down the particle size as it contains piezoelectric quartz crystal, which can expand and contract according to an alternating electric voltage. It is mainly used in laboratories where an emulsion droplet size as low as 0.2 μm can be produced [23]. A two-step mechanism has been suggested for ultrasound emulsification: First, interfacial waves are produced in anacoustic field to break the dispersed phase into a continuous phase. Then, the formation of acoustic cavitation collapses micro-bubbles into smaller droplets through the pressure fluctuations.

Advantages:

1. Improve the emulsification effect of emulsifier.
2. Enhance emulsion stability.
3. Control emulsion type.
4. Low power consumption of emulsifier.

Nanoparticles: There is a new interest in making nanoparticle stabilized nanoemulsions. A considerable number of nanoparticle formulation methods are based on NE templates, which in turn are generated in various ways. It must, therefore, be taken in to account that the active principles and drugs encapsulated in nanoparticles can potentially be affected by these NE formulation processes [44].

Such potential differences may include drug sensitivity to temperature, high-shear devices, or even contact with organic solvents. Likewise, NE formulation processes must be chosen in light of the function of the selected therapeutic goals of the nano-carrier suspension and its administration route. This requires the nanoparticle formulation processes (and thus the NE formation methods) to be more adapted to the nature of the encapsulated drugs as well as to the chosen route of administration [45, 46]. If the oil has the right properties and a sufficient concentration of nanoparticles, then water drops self-disperse within the oil.

Advantages:

1. Nanoparticles drug carriers have higher stabilities.
2. Nanoparticles have higher carrier capacity.
3. Feasibility of variable routes of administration.
4. Nanoparticles can also be used for controlled delivery of drugs.
5. Nanoparticles are non-toxic and capable of being stored for longer periods.

High Shear Mixers: High shear mixers have been widely used in energy intensive processes such as homogenization, dispersion, emulsification, grinding, dissolving, and cell disruption in the fields of agricultural and food manufacturing and chemical reaction processes. High shear mixers are available in both batch and inline configurations. Batch units will have radial or axial discharged types, while for inline high shear mixers, they have either a blade screen or a rotor stator teethed configuration. Batch high shear mixers can be used together with inline high shear mixers where the inline unit functions in a circulation loop downstream of a tank equipped with the batch unit. This can further improve the product quality and decrease the processing time. They consist of a rotor that turns at high speed within a stationary stator. When the rotor rotates, the substance or emulsion will continuously attract into the mixing head and will be ejected through the stationary stator in high velocity. The size of the droplets will decrease as the hydraulics hear mixes the emulsion faster [50].

Low Energy Emulsification Methods: Similar droplet sizes can be achieved while using both the low and high energy methods, which relies on the system and composition variables. However, it has also been claimed that high energy methods allow for the preparation of NEs with higher oil-to-surfactant ratios compared with low energy methods [50]. However, NEs with high oil-to-surfactant ratios prepared by low energy methods have also been reported. Low energy methods, unlike the high energy methods, are ruled by the behaviour of the systems and intrinsic physicochemical properties. It follows therefore that high energy methods present natural predispositions to preserve the formation processes of NEs droplets, against even the smallest possible alterations of the formulation such as the incorporation of the initiator, surfactant, monomer, and others [41, 42].

Phase Inversion Temperature Method: In the phase inversion temperature method (PIT), NEs are spontaneously formed by changing the temperature time profile of the components, and prompt temperature changes hinder the occurrence of coalescence and thus, the formation of stable NEs. At room temperature, the combination of oil, water, and non-ionic surfactant demonstrates a positive curvature. The impact of surfactant concentration on the formation and stability has been reported in previous work [43– 46]. Furthermore, the PIT method is based on the alterations in the dispersity of polyoxyethylene- type nonionic surfactants with temperature. With increasing temperature, these kinds of surfactants will turn lipophilic due to the dehydration of the polyoxyethylene chains. At low temperatures, the surfactant monolayer has a large positive spontaneous curvature forming oil-swollen micellar solution phases (or O/W microemulsions), which may coexist with an excess oil phase. At high temperatures, the spontaneous curvature becomes negative and water-swollen reverse micelles (or W/O microemulsions) coexist with an excessive amount of the water phase. At intermediate temperatures, the hydrophile lipophile balance (HLB) temperature and the spontaneous curvature tend to be zeroandbi-continuous, D phase microemulsion containing comparable amounts of water and oil phases that coexist with both excess water and oil phases is formed [47, 48].

Phase Inversion Composition Method: The relatively easy formation and low energy costs have given the phase inversion composition (PIC) method the great potential for scale-up applications. Furthermore, this process is more suitable for the emulsification of short-chain alkanes prepared at 25°C. When the PIC method is employed, a phase inversion occurs when the continuous phase is slowly mixed over the component that will create the dispersed phase [40]. In order to obtain small and uniform droplets, both phases need to cross the emulsification path, a zone where a liquid crystal (lamellar or cubic) or bi-continuous phase exists. Therefore, the dispersed phase is intimately mixed with the continuous one and, when an additional continuous phase is added to reach the final composition of the NE, a reorganization of the dispersed phase into small droplets is likely [41]. In the phase inversion method (PIC), chemical energy from the reaction of the components forms a fine dispersion, resulting from the phase transitions produced by the emulsification pathway. The phase transition is produced by varying the composition of the emulsion and keeping the temperature constant or vice versa. The phase inversion temperature was first reported by Shinoda *et al* [42]. It was concluded that the increase in temperature results in the chemical changes of polyoxyethylene surfactants through the degradation of the polymer chain with temperature [43].

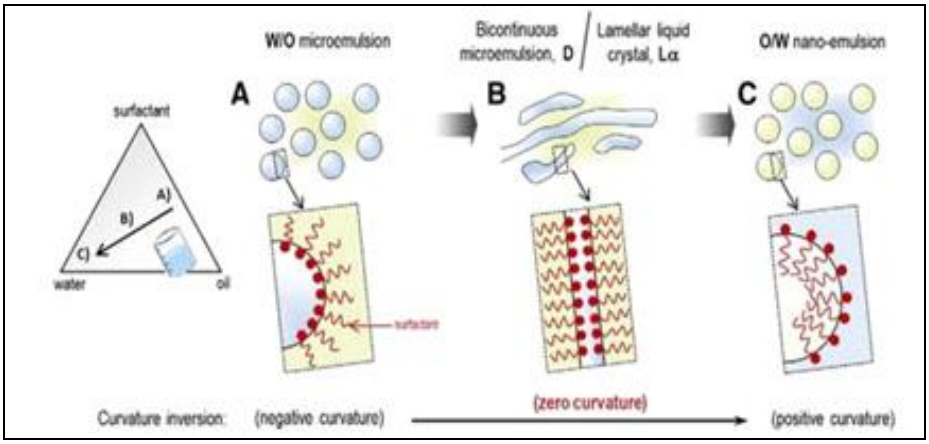

FIG. 5: SCHEMATIC REPRESENTATION OF PRODUCTION OF NES BY PIC

Spontaneous Emulsification: Spontaneous emulsification is another method in which nano-sized emulsion can be obtained. The chemical composition of both the oil and aqueous phases and the help of surfactants is really important in this technique [19]. Three stages are involved in this method, namely, (1) a homogeneous lipid phase consisting of oil and a lipophilic surfactant and another phase of a water- miscible solvent and hydrophilic surfactant were prepared; (2) the O/W emulsion is formed when the lipid phase is injected in the aqueous phase under nonstop magnetic stirring; and finally, (3) evaporation under reduced pressure is employed to remove the aqueous phase [24]. A nanoemulsion will be obtained by the dilution of the microemulsion with water. From the oil/ water interface, the cosurfactant (alcohol) diffuses to the water phase, which will disturb the formation of the microemulsion and make it thermodynamically unstable, thus forming NEs [41].

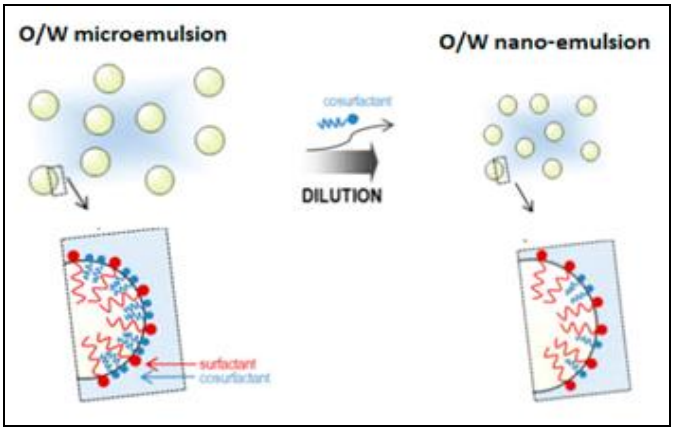

FIG. 6: SCHEMATIC REPRESENTATION OF THE SELF EMULSIFICATION METHOD BY THE DILUTION OF AN O/W MICROEMULSION

Solvent Displacement Method: The solvent displacement technique is also known as the nanoprecipitation method. This method is based on the interfacial deposition of polymeric nanoparticles after the displacement of a semi-

polar solvent that is miscible with water from a lipophilic solution [46]. Polymeric nanoparticles can be obtained from nanoemulsions either by in situ monomer polymerization in the dispersed phase or using a preformed polymer (dissolved in a volatile organic solvent) as the dispersed phase of the nanoemulsion, followed by solvent evaporation [47]. This method can produce NEs using only simple stirring at room temperature and is used for parenteral preparation. However, the drawback of this method is that it produces small-sized emulsions of the dispersal phase, where this method acquired a large ratio of solvent and oil. Nevertheless, for the preparation of monodisperse, small-sized polymeric nanoparticles, this technique is a totally convenient, reproducible, fast, and economic one-step manufacturing process [39].

Evaluation Parameters of SNEDDS:

Thermodynamic Stability Studies: The physical stability of a lipid based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well. In addition, incompatibilities between the formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug.

Heating Cooling Cycle: Six cycles between refrigerator temperature (4°C) and 45°C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

Centrifugation: Passed formulations are centrifuged thaw cycles between 21°C and +25°C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30min. Those formulations that does not show any phase separation retaken for the freeze thaw stress test.

Freeze thaw Cycle: Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility Test: The efficiency of self-emulsification of oral nanoemulsion is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation was added to 500 ml of water at 37 ± 0.5°C. A standard stainless-steel dissolution paddle rotating at 50rpm provided gentle agitation. The *in-vitro* performance of the formulations is visually assessed using the following grading system.

Grade A: Rapidly forming (within 1 min) nanoemulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish white appearance.

Grade C: Fine milky emulsion that is formed within 2 minutes.

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 nano-emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SNEDDS formulation [24].

Droplet size Analysis and Particle size Measurements: The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in lights cattering due to Brownian motion of the particles) using a Zetasizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25°C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water which proves the system's compatibility with excess water [25, 26].

Zeta Potential Measurement: This is used to identify the charge of the droplets. N conventional SNEDDSs, the charge on an oil droplet is negative due to presence of free fatty acids.

Refractive Index and Percentage Transmittance: Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by refractometerby placing a drop of

solution on slide and it is compared with water (1.333)**.** The percent transmittance of the system is measured at particular wavelength using UV-spectrophotometer keeping distilled water as blank. If refractive index of system is similar to the refractive index of water (1.333) and formulation have percent transmittance> 99 percent, then formulation have transparent nature.

***In-vitro* Diffusion Study:** *In-vitro* diffusion studies are performed for all the formulations developed, using a dialysis technique. The dialyzing medium such as phosphate buffer pH 6.8 is used. One end of pretreated cellulose dialysis tubing (7 cm in length) is tied with thread, and then 1ml of self-nanoemulsifying formulation is placed in it along with 0.5 ml of dialyzing medium.

The other end of the tubing is also secured with thread and was allowed to freely in 200 ml of dialyzing medium and stirred continuously at100 rpm with magnetic bead on magnetic plate at 37°C. Aliquots of 1 ml are removed at different time intervals and diluted further. Volume of aliquots is replaced with fresh dialyzing medium each time. These samples are analyzed quantitatively for drug dialyzed across the membrane at corresponding time by using UV-visible spectrophotometer.

Drug Content: Drug from pre-weighed SNEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract is analyze by suitable analytical method against the standard solvent solution of drug [27, 28].

Advancements in SNEDDSs:

Supersaturated SNEDDSs: Drug solubility in lipidic components is the key factor that determines the dose of a drug to be administered in a SNEDDS formulation. As the oil content is reduced during the dispersion or digestion, the solubilizing capacity of SNEDDSs declines *in-vivo*, leading to drug precipitation. Therefore, most SNEDDSs contain drugs below their equilibrium solubility, typically between 50% and 90%, limiting the access of many drugs to this promising technology, especially drugs that should be given at a high dose. To overcome this drawback, supersaturated SNEDDSs (s-SNEDDSs) containing precipitation inhibitors have been suggested. s-SNEDDSs are thermodynamically stable SNEDDSs containing a polymer (such as poly vinyl pyrrolidone (PVP) or hydroxypropyl methyl cellulose) that should inhibit the nucleation process and subsequent drug precipitation, thus temporarily maintaining a supersaturated solution of the drug in the GI tract. Super saturation enhances the thermodynamic stability of the drug above its solubility limit, thus improving both the extent and rate of drug absorption. Moreover, the higher drug loading in the formulation increases the flux over the GI epithelium.

Mucus-Permeating SNEDDSs: Due to faster clearance rates and rapid secretion, the mucus barrier sets a challenge for conventional drug-delivery systems to reach the GI epithelial cell surface and remain there for a sufficient amount of time.

It has been reported that SNEDDSs composition and resulting nano-emulsion droplet size are the most important factors influencing the mucus-permeating ability of a SNEDDS formulation. Most SEDDSs formulations contain surfactants made of PE Gylated groups to ensure self-emulsification process, so their relatively high mucus-permeating abilities can be explained by those PE Gylated groups located at the surface of the oil droplets, making SNEDDSs highly muco-inert.

Currently, several strategies are used to improve mucus permeation of SNEDDSs, including surface charge modification, mucoadhesive polymer and the inclusion of mucolytic agents. SNEDDSs that can change their zeta potential from negative to positive were formulated. The advantages of this approach are that negatively charged SNEDDSs formulation can diffuse more quickly across the mucus gel layer, and zeta potential are shifted to positive once in contact with GI epithelium, allowing improved cellular uptake.

Solid SNEDDSs: Despite the benefits provided by liquid SNEDDSs, drawbacks such as drug/components precipitation when stored, interactions between the filling and the capsule shell, and formulation stability during storage are common issues faced by them. The main strategy applied to overcome these challenges is to transform liquid SNEDDSs into solid dosage SNEDDSs formulations. It is believed that the

conversion of liquid SNEDDSs to solid SNEDDSs provides relatively lower production cost, better formulation stability, ease of handing, precise dosing, and, consequently, better patient compliance.

Generally, the techniques employed to develop solid SNEDDSs include adsorption onto inert carriers, spray drying, melt granulation and extrusion-spheronization.

Targeted SNEDDS: Drugs in clinical trials may fail to reach favourable outcomes because they cannot target a desired site of action. A successful strategy to overcome this issue is to develop targeted drug-delivery carriers that release the drugs at a specific site of action. SNEDDS can be considered for this approach. Surface-modified nano-emulsions have been developed to reach animals and human liver in a similar way to chylomicrons.

SNEDDS can drastically increase the concentration of the drug in liver and/or spleen and can be a smart way to reach these organs. Another key aspect of SNEDDSs is their ability to be taken up into the lymphatic system. Many diseases, including, HIV, lymphoma, autoimmune diseases, leukemia, tissue rejection and tumormetastatis, require the lymphatic system for their progress. Furthermore, passive and active targeting is achievable by attaching suitable ligands (antibodies, nucleic acid or peptides) to target a specific site of action.

CONCLUSION: SNEDDS is a promising approach for BCS class II, class IV and drug compounds with poor aqueous solubility. The method used for lipophilic drugs resulting emulsification gives faster dissolution rate. The oral delivery by hydrophobic drugs can be made possible by SNEDDS which have been shown in substantially improved oral bioavailability with future development of this technology.

SNEDDS will continue to enable novel application in drug delivery and solve problems associated with the delivery of poorly soluble drugs. Previously, SNEDDS formulations were used to overcome issues related to low aqueous solubility and oral bioavailability of drugs. However, the scope of SNEDDS is far beyond the solubility and dissolution issues. Presently, they have evolved into mucus permeating, supersaturated, solid and targeted SNEDDS to tackle issues related to classical SNEDDS and to make new changes for several applications. Many anticancer, anti-diabetic, and anti-viral drug solubility, stability, and bioavailability characteristics were improved *via* SNEDDS formulations.

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