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A REVIEW ON SELF-NANO EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Self-emulsifying drug delivery system is categorised on factors such as size of droplets acquired after dispersion. Self-Micro Emulsifying Drug Delivery Systems (SMEDDS) are defined as having a droplet size of dispersion between 100 and 250 nm, whilst Self Nano Emulsifying Drug Delivery Systems have a droplet size below 100 nm. SNEDDS are isotropicmixtures of natural or synthetic oils, surfactants, and cosurfactants that have the unique abilityto form fine oil in water (O/W) nano-emulsions of approximately less than 100 nm upon dilution with water upon mild agitation. A SNEDDS formulation can be optimised through a phase diagram approach or statistical design of experiment. SNEDDS improve the oral bioavailability of hydrophobic drugs by several mechanisms. The self-emulsification time, dispersibility study, average globule size, and Poly dispersibility index (PDI) of the produced formulation were all examined. The globule size of the optimised system will be less than 100nm, which could be an acceptable nano emulsion range.

KEYWORDS: Self nano emulsifying DDS, oil, surfactants, statistical design of experiment, Polydispersibility index, bioavailability.

I. INTRODUCTION

The oral route has long been the preferred approach for formulators, dominating over alternative administration routes. The only drugs that can be administered by such a preferred route are those that have molecules that can pass through the gastric mucosa and are at least marginally soluble. 40% of novel chemical entities have poor aqueous solubility and pose a

significant challenge to the current drug delivery method. There has been an increase in interest in the formulation of poorly water-soluble medications in lipids as the rate of absorption might be improved by co administered with a diet rich in fat.[1]

Nanotechnology is widely acknowledged as a critical medication delivery strategy that can impact how well hydrophobic medicines work effectively. The implementation of self-nanoemulsifying drug delivery systems (SNEDDS) is one of the tested methods for enhancing the solubility and bioavailability of drugs that are not highly water soluble.

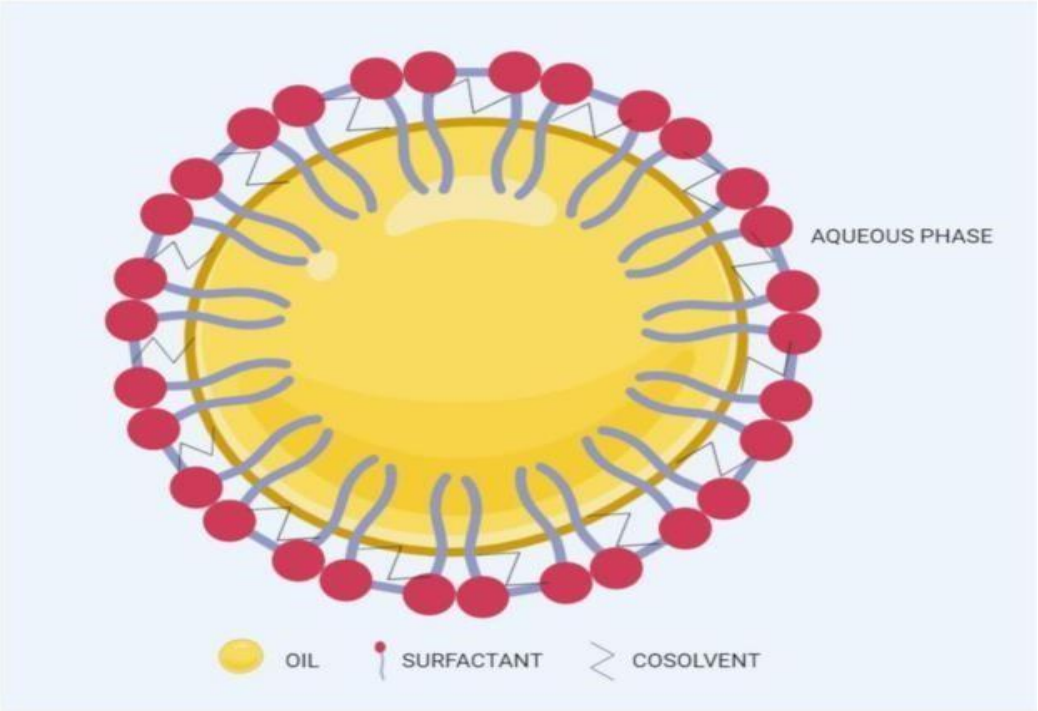


Fig: Typical structure of SNEDDSs after aqueous dispersion.

Nano emulsion preconcentrates or anhydrous nano emulsions are self-nanoemulsifying drug delivery systems (SNEDDS). The gastrointestinal tract could quickly digest and absorb drugs because of the nanosized SNEDDS. Due to the medication being pre-dissolved, SNEDDS can eliminate the fundamental rate-limiting stage of dissolution. Consequently, a rapid onset to action was attainable.[2]

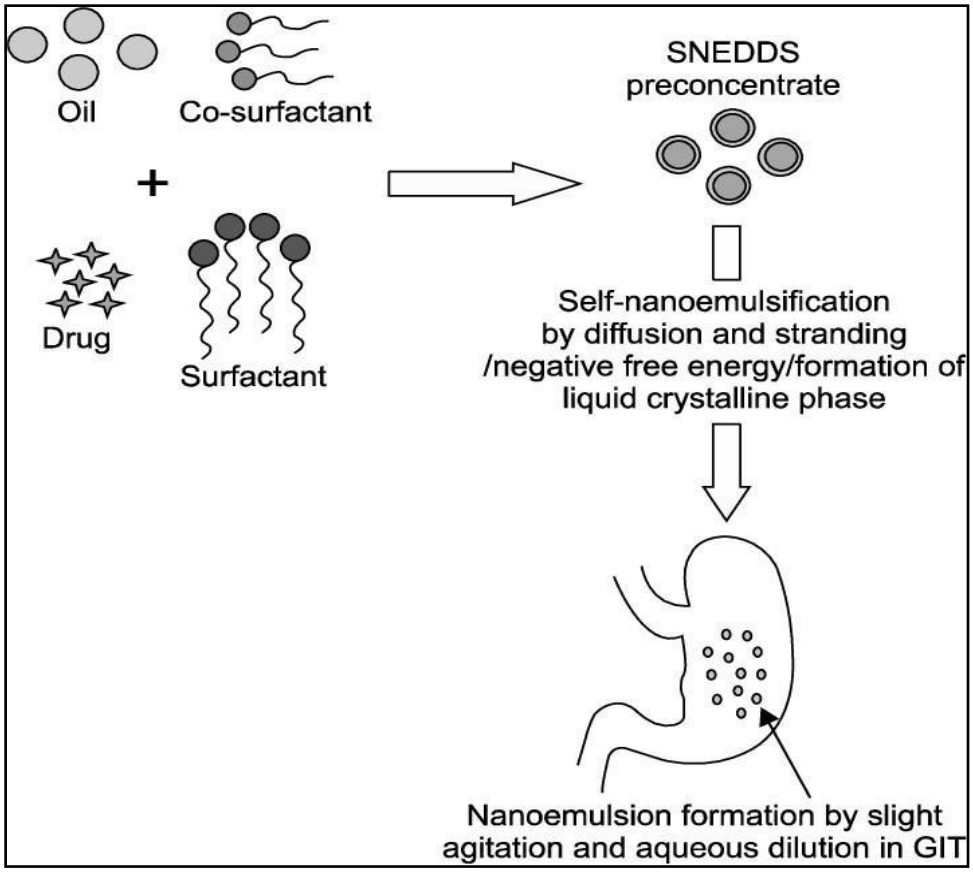
Self-nanoemulsifying drug delivery systems (SNEDDS), typically composed of an isotropic composition of oil, surfactant, co-surfactant, and drug. Upon administration, this isotropic composition will interact with the aqueous phase of gastrointestinal tracts and, with the help of gastrointestinal motility, generate an oil-in-water emulsion at a nanoscale range. This stable emulsion potentially offers a significant interfacial area for drug partitioning between oil and

water phases, perhaps enhancing bioavailability and solubility rate. Although SNEDDS only needs basic and affordable manufacturing facilities, it seems like a suitable formulation selection.

This is as a result that SNEDDS is a lipid solution that is physically stable and eliminates the need for high energy source emulsification techniques. Additionally, a smaller therapeutic dose as well as possibly the omits dose-related adverse effects are implied by SNEDDS' improved dissolution rate and more consistent bioavailability. technique. Additionally, a smaller therapeutic dose as well as possibly the omits dose-related adverse effects are implied by SNEDDS' improved dissolution rate and more consistent bioavailability.[3]

In Self Nano emulsifying drug delivery systems

1. Oil droplet size is: 12
2. Appearance is optically clear Required
3. HLB value is >12
4. Oil Conc.: ‹20%.[4,5]



Schematic Diagram: Intestinal drug transport mechanism after ingestion of lipid based SNEDDS dosageform.[6]

II. TYPES OF NANOEMULSION (SNEDDS)

1. (W/O) Nano emulsion which has a continuous oil phase and droplets of water was dispersed in it.
2. (O/W) Nano emulsion which has a continuous water phase and a droplet of oil was dispersed in it.
3. Bi-continuous Nano emulsion in which both oil & water both solublises the surfactant,and droplet was dispersed in both Oil as well as water phase.[7,8]

- **Advantages of SNEDDS**

1. Prevention of sensitive drug substances.
2. Drug(s) are selectively targeted to a certain GIT absorption window.
3. Improved oral bioavailability facilitating dose reduction.
4. It is simple to store as it probably belongs to a stable thermodynamic system.
5. Scalability and manufacturing efficiency.
6. Reduction of nutritional effects and intra- and inter-subject variability.
7. The capacity to transport peptides in the GIT that are susceptible to enzymatic degradation.
8. The process of fat digestion is maintained.
9. Providing resources enabling drug uptake.
10. It's sterilisable.
11. High drug payloads.[9,10]

- **Disadvantages of SNEDDS**

1. The formulations cannot be evaluated using conventional dissolution methods because they may be dependent on digestion before the drug is released. Therefore, there are no reliable predictive in vitro models available.
2. To replicate this, an in vitro model which mimics the duodenum's digestive functions has been established.
3. Different prototype lipid-based formulations must be created and put to the test in live animals using an appropriate animal model.[11,12]

- **MECHANISM OF SNEDDS**

Reiss asserts that self-emulsification occurs when the energy needed to expand the surface area of the dispersion is larger than the entropy shifts that favors dispersion. The energy needed

to produce a new surface between the oil and water phases directly determines the free energy of the traditional emulsion, which can be expressed by the

DG= S N p r 2s..... (Equation 1)

Where,

DG = free energy related with theprocess,

N = number of droplets,

R = radius of droplets,

S = interfacial energy.

The emulsion is stabilised by emulsifying chemicals, which produce a monolayer of emulsion droplets and so reduce the interfacial energy as well as acting as a barrier to prevent coalescence. The two phases of the emulsion tend to separate over time to minimise the interfacial area. The requirement for a certain surfactant mixture that permits spontaneous emulsification may be linked to a reduction in the phase inversion temperature, which would make emulsions easier.[13]

- **Factors affecting SNEDDS**

1. Choosing the right emulsifying system (surfactant) to achieve the ultra-low interfacial tension that is essential for producing a stable nano emulsion system.
2. The dispersed phase must be extremely insoluble in the dispersed medium to prevent Ostwald ripening.
3. To stabilise the Nano emulsion, the surfactant must be utilised at its optimum concentration.[14]

- **CATEGORIZATION OF SNEDDS**

1. L-SEEDS (Liquid-Self Emulsifying Drug Delivery System) (Liquid-Self Emulsifying DrugDelivery System)

These are liquid, isotropic, self-emulsifying mixtures of surfactant, co-surfactant, and oil. It offers improved lymphatic absorption and better drug solubility. Conversely, as they are liquid, they are challenging to administer as a dosage form. They must be introduced in gelatin capsules to implement the dose form more convenient. In turn, this elevates the cost of formulation.

2. Super saturable SEDDS

Surfactant concentrations in SEDDS formulations differ considerably from 20 to 60%. As

their higher concentration is known to have some devastating results, utilising such a high concentration of surfactant raises safety issues for the formulator. In order to eliminate this issue, the proposal of super saturable SEDDS was developed. These contain a water-soluble polymeric precipitation inhibitor that lowers the concentration of surfactants (PPI). These formulations prevent drug precipitation utilising PPI, preserving a super saturable metastable state in vivo. It has been extensively documented that HPMC in various viscosity grades acts as a PPI in super saturable SEDDS to prevent crystallisation.

3. S-SNEDDS (solid Self Emulsifying Drug Delivery System)

Initially, self-emulsifying drug delivery systems were developed in liquid form. However, these L-SEDDS experienced challenges with stability, unit dosage S-SEDDS are a better alternative to L-SEDDS. S-SEDDS, along with the potential benefit of L-SEDDS, provide improved stability, convenience in handling, and compatibility with traditional dosage forms such as tablets and capsules.[15]

- **COMPOSITION**

The self-emulsifying process depends on

- The oil and surfactant's nature.
- The concentration of surfactant
- The temperature at which self-emulsification occurs.

1. Oil

Water is the most significant vehicle and oil comes second, as it has an ability ofsolubilizing the molecules of lipophilic drugs and also helps in improving the absorption by lipid layer present in the body. Oil is very useful for lipophilic active delivery of drug due to its unique ability to penetrate cell walls. The oil phase influences the swelling of the tail group region of surfactant. In comparison to long chain alkanes, short chain alkanes have better penetration.

2. Surfactant

The surfactant has a positive influence on the emulsification process, the nano- emulsifying zone, and droplet size. HLB in oil, viscosity, and affinity to oil phase are some of the characteristics that need to be taken into consideration. Surfactants are screened based on their capacity for emulsification by combining oil and surfactants in heated circumstances, followed by diluting the resulting isotropic mixtures with deionized water. Following the actual accomplishment of equilibrium, the % transmittance can be evaluated using a

spectrophotometer, and droplet size and the polydispersity index were determined using a zeta Sizer. The emulsion's droplet size is influenced by the surfactant's concentration. At greater doses, these surfactants may irritate the skin and GI mucosa. It is also vital to consider if the surfactant is suitable for the specific route of administration because it often could have negative influences.

3. Cosurfactant

The surfactant unit and co-surfactant both serve comparable purposes. Co-surfactant was added to a surfactant unit or mixture of surfactant units to augment the surfactant's ability to improve the water solubility of pharmaceuticals with weak water solubility. The co-surfactant is a unit of single chain surfactant that can prevent interfacial fluidity. The monomolecular layer of the surfactant molecule can separate the co-surfactant molecule from the surfactant, oil, and water molecules.

Liquid Crystal Formation Layer is the name given to the monomolecular layer of the surfactant molecule. Cosurfactants include substances such as ethanol, methanol, pentanol, glycol, and propylene glycol33. They are introduced in SNEDDS to reduce interfacial tension at the oil-water interface. Co-surfactants are employed to enhance the surfactant's emulsification. They are additionally screened by developing isotropic mixtures by combining several co-surfactants with a specific surfactant and oily phase under warming conditions.[15,16,17]

III. TECHNIQUES OF SNEDDS

A. High Energy Emulsification Method

1. High pressure homogenization (HPH)

High pressure homogenization is required to produce a nano emulsion system. The primary tool utilised in this technique to create nano emulsions with incredibly small particle sizes was a high-pressure homogenizer or piston homogenizer (up to 1 nm). When two phases (oil and aqueous phase) are forced through a small inlet orifice at a high pressure (500 to 5000 psi), the product is subjected to extreme turbulence and hydraulic shear, forming incredibly tiny emulsion particles.[18]

2. Ultrasonication

Ultrasonic emulsification is a highly effective technique for lowering droplet size. This technique uses sonotrodes referred known as Sonicator probes to deliver the energy. It might

include quartz crystals that respond to alternating electric energy by expanding and contracting, or piezoelectric crystals.

When the Sonicator's tip makes contact with a liquid, mechanical vibration and cavitation can develop. Cavities generated by cavitation and their collapse in liquid. So, emulsion can be created by ultrasonic directly. This approach may produce emulsion droplets as small as 0.2 mm, making it mostly useful for lab applications.

3. Micro fluidization

Micro fluidization is a proprietary mixing technology that employs a device known as a microfluidizer. The product is forced through the interaction chamber by the device's high pressure positive displacement pump (500–20,000 psi), generating very small particles in the submicron range. This procedure is carried out numerous times to achieve a uniform or homogeneous nano emulsion system of the appropriate size.

B. Low Energy Emulsification

1. Phase inversion emulsification method

By increasing the temperature of the whole emulsification process, this approach includes phase transformation.

2. Spontaneous emulsification

Nano emulsion is generated spontaneously in this process. It involves creating a consistent, homogeneous organic solution with a hydrophilic and a water-miscible surfactant phase, as well as oil and a lipophilic surfactant. Under continuous magnetic stirring, the organic phase was poured into the aqueous phase, forming stable o/w. Under low pressure, the aqueous phase was eliminated by evaporation.[19]

IV. EVALUATION PARAMETER OF SNEDDS

1. Thermodynamic stability studies

A. Heating cooling cycle: The performance of a lipid-based formulation depends on its physical stability, which could be negatively impacted by drug precipitation in the excipient matrix. However, a lack of formulation physical stability can cause the excipient to phase separation, which will damage both the formulation's functionality and appearance.

Brittleness, distortion, a delay in disintegration, or insufficient drug release can alsoresult from

incompatibilities between the formulation and the gelatin capsule shell.

B. Centrifugation: Six cycles between 4°C and 45°C are evaluated, with storage at each temperature lasting minimum 48 hours. Those formulations that can withstand these temperatures are put through a centrifuge test.[20]

C. Freeze thaw cycle: The formulations involve three freezes. The formulations that passed this test demonstrated excellent stability, with no phase separation, creaming, or cracking.

2. Dispersibility Test

- Grade A: a nano emulsion that forms quickly (in less than one minute) and appears transparent or bluish.
- Grade B: Rapidly generating, slightly less clear, and bluish-white emulsion.
- Grade C: A thin, milky emulsion that formed in less than two minutes.
- Grade D: A dull, greyish-white emulsion that seems slightly greasy and is slow to emulsify (longer than 2 min).
- Grade E: A formulation that has little to no emulsification and has noticeable big oil globules on the surface.

Grades A and B When dispersed in GIT, the formulation will remain as a nano emulsion, however a formulation failing in Grade C may be preferred for SEDDS formulation.

3. Droplet size analysis

Using a Zeta Sizer 1000HS, photon correlation spectroscopy was used to measure the droplet size of (SNEDDS), which analyses variations in light scattering brought on by the particle's Brownian motion (Malvern Instruments, UK). At 25 ºC, light scattering was observedat a 90º angle.

The particle's nanometric size range is maintained even after being diluted with water 100 times, demonstrating the system's compatibility with too much water.[21]

4. Zeta potential measurements

The colloidal stability is revealed by the zeta potential. By measuring the droplets' electrophoretic mobility, it is calculated. High zeta potential values (>40 mV) indicate the presence of repulsive electrostatic forces, which lower the probability of particle aggregation. The medicine contained in SNEDDSs can be absorbed orally differently depending on the nanoparticle charge. Concerning the enhancement of absorption, charge-dependent interaction with mucus and cell membrane barriers has been observed.

The particles will migrate toward the electrode with the opposite charge when a voltage is supplied to the electrode. To determine the particle velocity as a function of voltage, the Doppler method is utilised. The intensity of scattered light varies as particles move through a laser beam that is passing through the cell at a frequency proportional to the speed of the particles. The zeta This procedure is carried out numerous times to achieve a uniform or homogeneous nano emulsion system of the appropriate size.[22]

Table 1: Reference values of Zeta potential.[23]

Zeta potential [mV]	Stability behavior of colloid
0 to ±5	Rapid coagulation or flocculation
±10 to ±30	Incipient instability
±30 to ±40	Moderate stability
±40 to ±60	Good stability
> ±60	Excellent stability

5. Refractive index & % transmittance

The formulation's transparency was shown by its refractive index and percent transmittance. A refractometer is used to determine the system's refractive index by dropping a solution onto a slide and comparing it to water (1.333). spectrophotometer by UV is used to assess the system's % transmittance while utilising distilled water as a reference. If the system'srefractive index is similar to the refractive index of water (1.333) and the formulation has a percent transmittance greater than 99 percent; the formulation is transparent.[24]

6. Determination of self-emulsification time

Visual evaluation is the basic approach to self-emulsification assessment. At 37ºC15, the effectiveness of self-nano-emulsification is assessed by agitating a mixture of water and 0.1N HCl solution (100ml) at 100 rpm. The duration needed to produce a Nano emulsion depends on the amount of water introduced to SNEDDS.

7. In vitro diffusion studies

Using a dialysis method, in vitro diffusion studies are conducted to examine the behaviour of the drug formulation's release from the liquid crystalline phase enclosing droplets. The dialyzing solution is a pH 6.8 phosphate buffer. One ml of the self-nano emulsifying formulation and 0.5 ml of the dialysing medium were added to the pre-treated cellulose dialysis tubing's knotted end.

The other end of the tube is also threaded and allowed to freely rotate in 200 ml of dialysing

liquid while being stirred constantly at 100 rpm at magnetic bead on magnetic plate at 37 degrees Celsius. The 1ml aliquots that were taken at various times are further diluted. Each time, the volume of aliquots is changed with new dialysing media. The se samples underwent quantitative drug analysis.[25]

8. Drug content

A standard volumetric flask was filled with several formulations, each containing 10 mg, and methanol was used to combine and dilute it. 1 ml of this solution was diluted to 10ml with phosphate buffer yielding 100 g/ml (theoretical). The drug content was also determined using an RP-HPLC technique established at 246 nm.[26]

% Of drug = Standard peak area / Sample peak area**×100** Standard peak area at 100µg/ml

V. APPLICATIONS

1. Protection against biodegradation

SNEDDS, SMEDDS and SEDDS are significant for their ability to transport macromolecules such as peptides, hormones, enzyme substrates and inhibitors of enzymaticdegradation.[27]

2. Application in drug delivery

Nano emulsions are of tremendous interest both in pharmaceutical formulation as well as in nutraceuticals, food goods, and cosmetics formulation. Drugs can be delivered via nano emulsions in a number of ways, including parenteral, oral, topical, ocular, pulmonary,mucosal, cosmetic, transdermal, controlled, and target delivery.

Nano emulsion in cell culture technologyProphylactic in Bio-Terrorism attack Nano emulsion in cancer therapy Nano emulsion to enhance skin penetration.[28]

3. Efficient water solubility of hydrophobic drugs

The self-nanoemulsifying drug delivery system makes it possible for hydrophobic drugs to dissolve better in water and to have higher oral bioavailability.[29]

VI. CONCLUSION

Its simplicity in production and scaling-up sets SNEDDS apart from other novel drug delivery methods such solid dispersions, liposomes, and nanoparticles.

This can be employed soon to tackle difficulties linked to medication solubility and can be a

decent option for the same. SNEDDS appears as unique & industrial survival approach with future development.

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