

REVIEW ARTICLE

Self-Nanoemulsifying Drug-Delivery Systems: Development, advancements and opportunities in improving oral absorption

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ABSTRACT

Orally administered medication solubility is a key concern for the pharmaceutical business; about 35-40% of newly introduced pharmaceuticals have less aqueous solubility, resulting in deprived dissolution and limited bio-availability. Employment of lipid-oriented drug release methods like self-nano-emulsifying drug delivery system (SNEDDS), its use to progress drug solubility, permeability, & bio-availability has been extensively reported in literature. A SNEDDS is made up of an oil component, a surfactant & a co-surface active agent. SNEDDS are intended for a broad variety of applications because of their small droplets, high solubility, large interfacial region, low steadiness, transparent or semi-transparent appearance, and extraordinary kinetic reliability. Multiple orthogonal approaches are necessary for SNEDDS characterization in order to thoroughly organize SNEDDS manufacturing, strength, & biological release. The characterization of SNEDDSs includes multiple orthogonal methods required to fully control SNEDDS manufacture, stability, and biological fate. Encapsulating a drug in SNEDDSs can lead to increased solubilization, stability in the gastro-intestinal tract, and absorption, resulting in enhanced bio-availability. To improve efficacy and patient conformity, a supersaturated, mucus permeating, and tailored SNEDDS can be produced. The self-emulsification method has proven effective in oral medication delivery.

Keywords: Bioavailability, SNEDDS, oral delivery, solubilization, formulation.

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INTRODUCTION

Oral administration is preferred delivery due to its safe nature, patient agreement, & potential for individual administration. Though it's the most suitable method, it has been limited because of the multiple barriers of gastro intestinal (GI) tract [1, 2]. Dissolving inside GI tract is required for absorption, as inadequate dissolution may result in incomplete absorption, less bioavailability, & significant inconsistency after oral release [3]. Lipid oriented preparation is a feasible method for improving aqueous solubilization & enter corporation of lipid-based medicines. Primary purpose is to maintain medications as solution in GI tract [4]. Self-nano emulsifying drug delivery systems (SNEDDSs) are researched (lipid-based drug release systems) in oral medication delivery. SNEDDS is uniform blend of oil, surfactants, & co-surface-active agents having an extraordinary capacity for creating fine oil-in-water (O/W) nano emulsions in the company of aqueous media when agitated moderately. It has a drop size range of >100 nm when dispersed in water [5-7]. To date, several researches have focused on the SNEDDSs application for the oral path of lipid-oriented substances, but few have introduced the probable of SNEDDSs to improve oral transport of aqueous soluble macromolecules. Current publication provides a thorough review of SNEDDS progress, characterization & *in vitro* testing.

ADVANTAGES OF SNEDDS

- Because they are nanosized, SNEDDS are a viable substitute to more traditional lipophilic compound oral formulations.
- It is predictable to emulsify swiftly in watery contents of abdomen. As a result, the medicine is introduced in solution within nanosized oil droplets. These small droplets would be evacuated from the stomach quickly, leading in quicker medication release throughout the GI tract.
- SNEDDS gives the medicine a substantially wider interfacial region intended for partitioning among oil & water, ensuing in easiness of dissolvability [8].
- Do not rely on the act of enzymes, bile salts or additional actions connected to the stomach's (fed/fasted) condition.
- SNEDDS minimize unpredictability in absorption rate & extent, and provide predictable plasma levels.
- Improved physico-chemical stability, as well as the facility to pack into forms like capsules, enhance economic feasibility, patient conformity/acceptability, and minimize palatability difficulties.
- An important component is its capacity to keep dosage in solubilized form all through GIT designed for long enough for absorption [9].

DISADVANTAGES SNEDDS

- A high concentration of surfactants/co-surfactants is required for stabilization, and temperature & pH have an effect on its steadiness.
- The Oswald ripening outcome could lead to instability.
- Expensive procedure. [10, 11]

This review focuses on several aspects of the SNEDDS are highlighted in this review, involving method of preparation, techniques for characterization, advantages, disadvantages, a special emphasis on applications of SNEDDS in various areas.

MECHANISM OF SELF-EMULSIFICATION

When entropy shift which favors scattering/emulsification is larger compared to energy crucial to amplify surface occupancy of dispersion, emulsification takes place. Typical emulsion's free energy is a straight consequence of energy necessary to set up a fresh surface among the oil & aqueous phases. Following equation describes this [12].

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

Where, ΔG ; free energy, N ; number of droplets of radius r & σ indicate sinter-facial energy. Because power necessary to construct the emulsion in SNEDDS is very less, emulsification procedure could occur spontaneously [13].

After ingestion, followed by modest agitation caused by gastrointestinal motions, the SNEDDS creates an o/w nanoemulsion with nanometric particles (200 nm) instantly and impulsively [14]. By changing the transfer property, the amplified interfacial area improves drug solubility & permeability [15].

Nanosize droplets disintegrate quickly, allowing for faster medication absorption into the GI system (Figure 1). The SNEDDS dose ranges from 25 mg to 2 g. [16] These are efficiently encapsulated to provide improved stability, palatability, and patient acceptance [17].

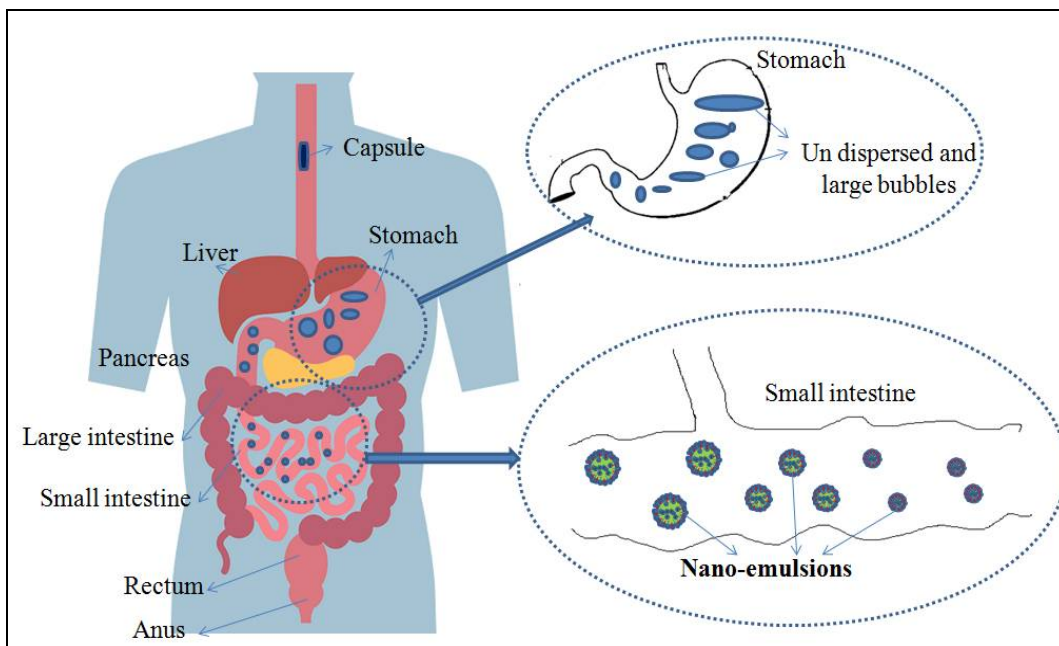


Figure 1: Mechanism of self-emulsification in biological system

Self-nano emulsifying composition

The elements that follow have a role in the assembly for the SNEDDS & ought to be considered, as shown in Figure 2.

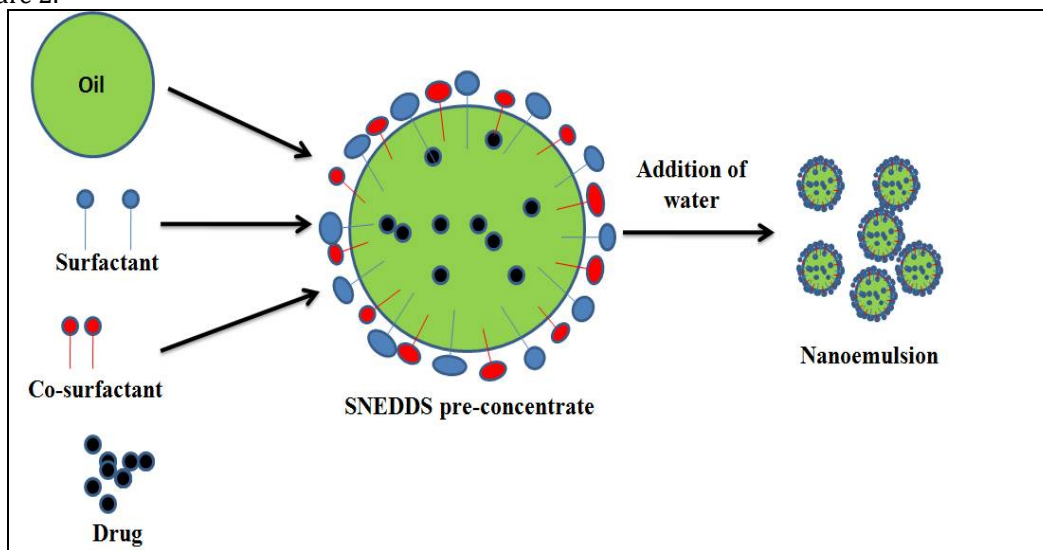


Figure 2: Self nano emulsification

Oils

Choosing right oil is critical as it influences collection of rest of nanoemulsion composition, especially in o/w nanoemulsions. Oil with high Solubilizing capacity contributes to achieving greatest drug load in nano emulsions [18]. Triglycerides are naturally occurring fatty acids with series of lengths & degrees of unsaturation. Capacity of oily phase to solubilize medicines is a factor in choice of oily phase & the ease from which it can form a nano emulsion with required properties [19]. Frequently used oils for SNEDDS include soybean oil, castor oil, glyceryl monostearate, ethyl oleate, vitamin E, and oleic acid.

Surfactants

It must be able to micro emulsify lipid component while still having strong solubility qualities for non-aqueous therapeutic compounds. The use of surfactants in the manufacture of nano-emulsions is critical. Surfactants with low hydrophilic lipophilic balance (HLB) values (like sorbitan monoesters) are water immiscible and generate a w/o nanoemulsion, whereas surface active agents having high HLB values (>10) form an o/w nanoemulsion [20]. Lipophilic core boosts the solution forming ability of the medication by entrapping it. When the lipid concentration is more, surfactants focus on oil/water

boundary, resulting in emulsions in which drug is soluble in inner oil component [21]. To generate nano emulsions, ionic or nonionic surfactants can be used; however ionic surface-active chemicals are unpreferred due to hazardous reasons. Surface active components such as lecithins, plaxomers, and polysorbate 80 are frequently used [22].

The accumulation of the droplet is related to quantity of surface-active agent utilized. In few situations, when utilizing a grouping of saturated C8-C10 polyglycolized glycerides, increasing the surfactant concentration can result in smaller droplets. On the opposing, raising the amount of surfactant may root the globule dimension to increase [23]. Surfactants include sorbitan monolaurate, Polyoxyethylene-20-sorbitan monooleate, Poloxamer (407 & 188), Polyoxyethylene 35 castor oil, and Tocopheryl PEG 1000 succinate are in use recently.

Co-surfactants

Surfactant unaided is regularly insufficient to decrease o/w interfacial force sufficiently to produce a nano emulsion, needing addition of a co-surface-active agent to get exterior pressure down \geq zero. At time when surfactant layer becomes too hard, co-surfactants go into the monolayer, increasing flow capacity and preventing the formation of liquid crystalline phases [24]. A very less HLB co-surfactant is often utilized in conjunction with an increased HLB surfactant to change total HLB of a system. Not like the surfactant, co-surfactant might not form self-associating structures on their own. Water soluble co-surfactants such as pentano1, hexano1, & octano1 have demonstrated to minimize oil/water interaction and assist impulsive nano-emulsion production [25].

Co-solvents

Surfactants should be present in comparatively high concentrations (typically < 30% w/w) to produce the best nanoemulsions. Ethyl alcohol, propylene glycol, glycerol, & polyethylene glycol (PEG) are appropriate intended for enteral release because co-solvency allows huge quantities of water loving surface active agent or drug to solubilize in the lipid & by assembling the adjacent hydrophobic phase & by declining water's dielectric constant [26].

Aqueous Phase

Composition of the aqueous component influences the globule diameter and consistency of nano-emulsions. As a result, when creating nano-emulsions, pH & ionic content of water phase should be accounted. pH levels in physiological system array from 1.2 to 7.4 & more (pH of blood & intestine). Electrolytes are well known to alter nanoemulsion features such as globule diameter and material consistency.

As a result, depending on the type of application, evaluating nano emulsion & its properties in water phases with varying pH & electrolyte quantities is a fine idea. In count to normal water, Ringer's, replicated stomach fluid, replicated intestinal fluid, & phosphate buffered saline may be utilized to analyze natural nano emulsification of SNEDDS. Such findings suggest that pH of hydro portion can show a significant impact on system's phase performance, particularly while a medication with a pH-dependent solubility is present [27].

Ternary phase diagram

Post selecting ingredients for SNEDDS, a ternary phase drawing among surfactant, oil, & co surfactant should be drawn to spot the emulsification area for determining the possible quantities of the excipients which prepare an impulsive nano emulsion. The self-nano emulsification area in this drawing is assessed through measuring the drop size post diluting a variety of ternary phase formulations with a fixed sum of water. [28] Self-nano-emulsification area is defined by the presence of spontaneous nanoemulsions with drop size > 200 nm. Ternary phase drawing is a 3-D plot that is presented in 2-D for ease of exposition & interpretation. Relative percentage of the composition is represented to demonstrate a sum of 100% or are normalized to 100%. [29] (Figure 3).

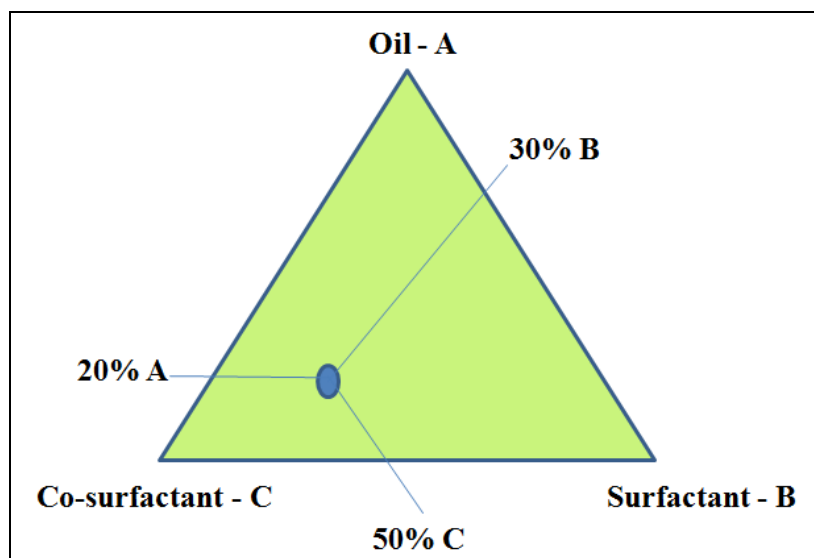


Fig - 3: 2D ternary phase drawing

SNEDDS can be optimized by means of a statistical experimental plan by analyzing the consequence of various variables on SNEDDS, like drop size, emulsification time & *in vitro* dissolution. After performing mathematical relationship among factors and the reaction is established, response surface design may be utilized for creating the desired produce [30].

Methods of preparation

Several ways have been developed in the direction of practicing nano-emulsion. However, developing a nanoemulsifying system needs a large quantity of energy. This can be obtained using by automatic apparatus or the element perspective within the constituent. Some of the ways used to create a SNEDDS include:

High Pressure Homogenizer

This works by applying a high level of stress on a composition containing a water phase, oil phase, surfactant/co-surfactant. Higher tension is created using homogenizer. Some of the problems related with homogenizers include decreased output and material fall as a result of excessive heat production. This approach can be used to make o/w nano emulsions with >20% oil content, but it cannot be used to make thick nano emulsions having a normal droplet thickness > 200 nm. [31]

Sonication Method

The droplet dimension of a common combination is compressed in this method by using a sonication procedure. This method can produce a restricted number of nano emulsion sets. [32]

Ultrasound Production using High Amplitude

This low-pressure homogenization could be employed in place of high-pressure homogenization. The strong trim forces required are provided by ultrasonic waves, which produce furiously & randomly imploding vacuity bubbles & shrink globule diameter towards the nano scale. On a limited scale, this method has been utilized to successfully manufacture nano-emulsions. [33]

Phase Inversion Method

Chemical energy might be employed to create excellent dispersion, which results in phase transitions when emulsified. Enough transition is generated by changing composition at a consistent temperature or altering the composition at a consistent heat. Phase inversion temperature technique is based on the response to temperature. As the heat rises, polymer chain dehydrates, causing surfactant to develop into lipid soluble. At declined temperatures, surfactant unit layer shows a significant +ve impulsive curvature, resulting in micellar form. [30]

Micro-fluidization

In micro-fluidization technology, a "micro fluidizer" is employed. Using a high pressure +ve displacement pump (500-200 PSI), the produce is pumped to interaction compartment having microscopic channels. Product moves all the way through microscopic pathways before impinging on a surface, resulting in submicron particles. In an aligned homogenizer, both solutions (aqueous phase & oily phase) are mixed & homogenized to form a crude emulsion. After that, this emulsion is processed in a microfluidizer to generate a steady nano-emulsion.[32]

Solvent Displacement Method

Oil phase will be mixed in water miscible organic solvents like acetone & ethanol in this technique. Through use of a rapid organic solvent, organic portion is mixed with aqueous part having surfactants, resulting in a nano-emulsion. Vacuum is utilized to separate organic solvent in the nano-emulsion. [31]

Evaluation

SNEDDS are evaluated for following factors:

Size & Polydispersity Index

A photon correlation spectroscopy approach used to quantify droplet dimension and polydispersity index (PI value). Test sample have to be disseminated in an appropriate solubilizing agent with adequate quantity & mixing is essential during sample groundwork [32].

Zeta Potential

Smoluchowski hypothesis is in use to calculate charge of nano emulsions. This parameter shows stability, formulation having an elevated zeta potential, especially if it is greater than 30 mv, it will remain stable [33].

Morphology

The shape & structure of nanoemulsion might be examined using TEM and SEM. TEM method offers knowledge on inner structure, whereas SEM method offers knowledge on surface of particle. Dilute samples have to be used for analysis [34].

Self-nano Emulsification Time

In general, at 37.5°C, SNEDDS (1 mL) is solubilized in water (250 mL). A paddle (50 rpm) provides gentle agitation. SNEDDS are evaluated based on emulsification pace & the finishing look. Point in time required for emulsification is recorded. Following emulsification, samples get analyzed for particle size by photon correlation spectroscopy & additional dispensation via various categorization [35].

Refractive Index (RI)

RI detects the clarity of the formulations. It is done by comparing the refraction of a small amount of the solution on a slide to water, with RI of 1.333. The composition is clear if the RI of the entire system is comparable to RI of water. RI is additionally employed for assessing the thermodynamic durability. The small variations in RI throughout the various storage times would imply that the SNEDDS have a constant structure and stability [36].

Percentage Transmittance

System's % transmittance is measured after diluting preparation (638 nm) using a UV-spectrophotometer & blank (water). If value approaches 100%, the formulation is plain and translucent [37].

Viscosity

A Brookfield viscometer can be in use to verify viscosity of SNEDDS in liquid form. Viscosity is expressed in centipoises [38].

In Vitro Dissolution

Employing type II dissolving apparatus, a SNEDDS *in vitro* solubilization pattern must be tested in different dissolution environments related with the intended route of treatment, like pH 1.2 & pH 6.8 for use by mouth. During a predetermined time period, the solubilized drug in would be withdrawn and analyzed with a suitable investigative method. The additive quantities of dissolved drug vs time would be graphed in comparison to pure drug [39].

Drug Loading Efficiency

The proportion of medicine encased in the particles can be established by combining a particular quantity of the preparation with an appropriate solvent which would tear the vesicles & disperse the medication to yield a specific volume. Magnetic stirrer can be used to agitate the ingredients for an appropriate amount of time. The resulting solution would then be collected and analyzed using a suitable quantitative technique. This can be determined from the below formula-

$$\text{Drug loading efficiency} = \frac{\text{Initial drug load} - \text{Amount of rug in the filtrate}}{\text{Initial drug load}} \times 100$$

Cloud Point Determination

This is a temperature at which nanoemulsion breaks down. To examine the steadiness of SNEDDSs in GIT, the cloud point is established. Distilled water is used to dilute the formulations, which are then kept in a water bath with a steadily rising temperature. Spectrophotometric studies will be performed to measure sample's transmittance. For SNEDDSs, temperature must be < 37°C; otherwise, medication incorporation

may be disrupted because cloudy emulsions affect the components employed in SNEDDS formulations [40].

Thermodynamic Stability Testing

This is conducted during the improvement stage to conquer the problem of metastable preparation. For 30 minutes, liquid SNEDDS are centrifuged (3500 rpm), a heating & cooling sequence applied to preparations those have not showed any phase partition for 6 cycles. Formulation which is still stable is then proposed to freeze-thaw test, which would consist of three 48-hour cycles (-21°C - 25°C). The preparation that passes this test can be chosen as a stable preparation [37].

Stability Evaluation

Stability should be studied in accordance with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) recommendations. Nontargeted nanomedicines, that are exempt from biotechnological product laws, must adhere to ICH Q1A(R2) & Q1C recommendations [36]. Furthermore, SNEDDS are defined by additional factors like micromeritic qualities. Hardness, weight fluctuation, friability, disintegration time, content uniformity, & *in vitro* release evaluations are some of the other criteria related with manufactured tablets of SNEDDS.

ADVANCEMENTS IN SNEDDS

Supersaturated SNEDDS (s-SNEDDS)

Drug loading is measured by level of solubility in the ingredients of SNEDDS. Solubilizing capacity of the SNEDDS is diminished by a decline in the lipid amount due to precipitation. The drugs that are solubilized in surfactants otherwise co-surfactants than in the lipids precipitate readily as solvent capacity decreases with dilution. The SNEDD formulations enclose medicines with solubilities less than equilibrium. Presence of significant quantities of water-soluble surfactants also aids medication precipitation.

Solid SNEDDS

Conservative liquid SNEDDS (L-SNEDDS) have a little limitation, like liquid drug to drug interface, drug to excipient interface, drug precipitation, higher cost, difficult manufacture, & management problems. Solidification of L-SNEDDS would overcome these limitations. These have enhanced solubility, bioavailability, effortlessness of manufacture, cheap cost, high reproducibility, stability, and scalability.^{31,32}

Controlled-Release Solid SNEDDS

Pharmacokinetic parameters for SNEDDS are analogous to recognized oral routed formulations. These produce quick absorption, increased C_{max} & less St_{max} , causing huge changes in drug quantity in plasma [33]. For which there is an increased need for progress of SNEDDS with prolonged & synchronized release qualities which does not compromise bioavailability [34].

When mixed nano emulsions were delivered at zero-order kinetics from tablet's exterior orifice, the medication was released in a controlled manner. HPMC, MCC, poly PLGA, and hydrophobic glacier are among the polymers utilized in controlled release SNEDDS formulations [35].

Mucus Permeation SNEDDS

Mucous barriers can be present in the nasal, lungs, ocular, vagina, & intestines [36]. The finest mucus infiltrating nanocarrier is believed to have SNEDDS. Due to their hydrophobic property, nanocarriers are anticipated to pass throughout the mucus membrane barrier without getting tangled in it. Considering the ability to penetrate in any composition, a particle with a diameter of 50 nm is ideal for mucosal infiltration [36, 37].

Bioactive SNEDDS

Due to increased selectivity & lesser toxic nature, biological molecules like protein, lipid, & polysaccharide are considered as current treatments [38]. Pharma research has been evolving using diverse protein, gene delivery, and bio-technology goods delivery technologies. The bigger dimension & limited penetrating capacity of biological molecules decrease their oral bioavailability, this could overcome by using SNEDDS, these shown to improve solubilization, diffusion, & bioavailability of biological molecules.

Self-Double Nano Emulsifying Drug Delivery Systems (SDEDDS)

Proteins & the popular cancer treating drugs are not intended to be taken orally. SDEDDS is recommended for administration of peptide & protein medicines.⁴¹ SDEDDS are water soluble surfactants that contain water in oil emulsions and form w/o/w emulsions when diluted using water & gently agitated. With greater competence and lower doses, SDEDDS protects peptides & medicines from inactivation (enzyme related) in the GIT.

Targeted SNEDDS

Targeted administration of drugs has the potential to enhance the effectiveness of treatment while decreasing toxicity. Small particles can elude mononuclear phagocytes & survive for a long time within the body. Droplets of cation were guided to an anionic based membrane obstacle. Targeted preparations are absorbed by liver and drug retention can also be accomplished with HPMC and thiolate chitosan [42].

Current Research

Hundreds of articles have been published for pharmacokinetics investigations using SNEDDSs in models like dogs, rats, & rabbits. Several SNEDDSs were developed & have demonstrated advanced *in vitro* & *in vivo* presentation in comparison to available medicines. Table 1 summarizes some preclinical studies that demonstrate improved bioavailability from SNEDDS formulations.

Table1: Current research on SNEDDS (pre-clinical studies)

Class	Drug	Composition
Anti-cancer	Docetaxel	Capryol [®] 90, Transcutol [®] HP, Labrasol [®]
	Erlotinib	Tween [®] 85, Dextran 40, Transcutol HP, Labrasol [®] , Aerosil 200, Labrafil [®] M2125 CS,
	Lycopene	LCT, Cremophor [®] RH, Tween [®] 85 Gelucire
	Methotrexate	Ethyl oleate, Tween [®] 80, Propylene glycol
Cardiovascular and anti-hypertensive	Carvedilol	Labrafil [®] M1944CS, Transcutol [®] , Tween [®] 80
	Clinidipine	Capryol [®] 90, Transcutol [®] , Tween [®] 80
	Rosuvastatin	Peceol [®] , Transcutol [®] HP, Tween [®] 80
	Valsartan	Triacetin or Castor oil, PEG 600
	Atenolol	Captex [®] , Tartaric acid, Oleic acid, Span [®] 80
Anti-diabetic	Insulin	Miglyol [®] , Cremophor [®] RH40, MCM C-10, Ethanol
	Exenatide	Capmul [®] -PG 8, Cremophor [®] EL, propylene glycol, Labrafil [®] 1944
	Trans-cinnamic acid	Cremophor [®] EL, Isopropylmyristate, PEG400
Antioxidant	Resveratrol	Miglyol [®] 812, Montanox, Labrasol [®] , Gelucire [®]
	Coenzyme Q10	Witepsol [®] H335, Solutol HS 15, Lauroglycol [®] FCC

CONCLUSION

SNEDDSs, contrasting to other lipid oriented nanocarriers like solid lipid nanoparticles (SLNs), nanostructured lipid carriers (NLCs), solid dispersions or liposomes, are able to be scaled up effortlessly by integration components using conventional tools. In addition, drug release connected concerns like a proclivity to coalesce while storage or while releasing the drug are unrelated to SNEDDSs as the fine dispersal is acquired instantaneously in the GI. As a result, SNEDDSs have higher medicinal characteristics for increasing solubility and oral bioavailability. More in recent times, the progress of marketed SEDDSs like Sandimmune[®] (cyclosporine), Fortavase[®] (saquinavir), Norvir[®] (ritonavir), and Neoral[®] (cyclosporine) has encouraged a growing curiosity in the employment of SNEDDSs to advance the solubility and bio-availability of the drugs.

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