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An Evaluation of the Self-Emulsifying Drug Delivery System (SEDDS)

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Abstract: *A self-emulsifying drug delivery system consists of a combination of surfactant, cosurfactant, and oil components that are emulsified in aqueous medium while being gently stirred and subjected to the digestive motility typically encountered in the gastrointestinal tract. One method utilized to enhance the oral bioavailability of hydrophobic medications is SEDDS. Solid dosage forms of liquid SEDDS can be produced without compromising the drug release characteristics. The micro/nano emulsified drug can be readily ingested via lymphatic pathways, circumventing the hepatic first-pass effect, due to its diminutive size. One significant advantage of this method is that the initial rate-limiting phase of particulate dissolution in the GI tract's aqueous environment is circumvented by pre-dissolving the compound. Self-emulsification takes place when the energy needed to increase the dispersion's surface area is less than the entropy changes that favor dispersion*

Keywords: Bioavailability, Lipid-based formulations, Drug solubility, Oral delivery

I. INTRODUCTION

In recent times, formulation scientists in the pharmaceutical industry have encountered intriguing challenges when it comes to the development of water-insoluble compounds. The pharmaceutical industry has identified that as many as 45% of newly discovered chemical entities are lipophilic or inadequately soluble compounds. This results in suboptimal oral bioavailability, considerable variation among subjects and within subjects, and an absence of dose proportionality. Diverse strategies, including solid dispersion preparation, co-precipitation, particle size reduction, and wetting agent application, have been employed in the oral formulation of these compounds in an effort to alter the dissolution profile and increase the absorption rate. Recently, lipid-based formulations have received increased attention as a means to enhance the bioavailability of medications that are inadequately soluble in water. Although there are numerous methods for delivering medications, including surfactant dispersion, emulsions, and liposomes, self-emulsifying drug delivery systems (SEDDSs) are among the most widely used. There are numerous methods for enhancing the rate and extent of drug absorption, including facilitating the absorption process and increasing the rate or extent of dissolution. In order to create a formulation that self-emulsifies, these methods are typically implemented.

SEDDS contain oil, surfactant, co-surfactant, and medication. SMEDDS are traditionally prepared by dissolving medicines in oils and mixing with solubilizing agents2. Oral absorption of highly lipophilic substances may be improved. SMEDDS are transparent micro emulsions with a droplet size of less than 50 nm and a concentration of less than 20% oil, compared to 40-80% in SEDDS. These physically stable formulations are easy to manufacture and can form fine oil-in-water (o/w) emulsions or microemulsions (SM).4. They create fine oil-in-water emulsions when gently agitated in water. Such mixes should self-emulsify soon in stomach aqueous media due to digestive motility5. SEDDS increase membrane fluidity to facilitate transcellular absorption, open tight junctions to allow paracellular transport, inhibit CYP450 enzymes to increase intracellular concentration and residence time by surfactants, and stimulate lipoprotein/chylomicron production by lipid6.

Oral administration of weakly water-soluble drugs via SEDDS appears promising. The chemical may be pre-dissolved in a solvent and filled into capsules. Oral hydrophobic medication delivery may be achievable using SEDDS. Most importantly, pre-dissolving the drug eliminates the first rate-limiting step of particle dissolution in the GI tract's aqueous environment. Using a hydrophilic solvent like polyethylene glycol may cause the medicine to precipitate out of

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solution as the formulation disperses in the GI tract. Since partitioning kinetics favor drug retention in lipid droplets, a lipid vehicle reduces the risk of GI tract precipitation.8. Two SELF systems exist10.

- Self-emulsifying drug delivery systems (SEDDSs).
- Self-micro-emulsifying drug delivery systems (SMEDDSs).

Different features of SEDDSs and SMEDDSs promote drug release. Simple binary systems with lipophilic phase, medication, or surfactant will be used in SEDDS formulations. Their droplets are 200nm-300nm and their dispersion is turbid. SEDDS contain 40–80% oil. SMEDDS are microemulsions made with a co-surfactant and have droplet sizes below 50nm with an optically clear-to-translucent appearance. SMEDDS has less than 20% oil. These systems (SEDDS) may improve oral bioavailability, allowing dose reduction, more consistent temporal profiles of drug absorption, selective targeting of drug(s) toward specific absorption window in GIT, protection from gut hostile environment, control of delivery profiles, reduced variability including food effects, protection of sensitive drug substances, high drug payloads, liquid or solid dosage formulation, ph.7-11. However, typical dissolve methods may not function since these formulations may need digestion before medication release. This in vitro model requires development and validation before being tested for strength. In vitro-in vivo correlations are difficult, hence prototype lipid-based formulations must be designed and validated in an appropriate animal model.12 Chemical instability of medications and excessive surfactant concentrations (30-60%) in formulations may disrupt the GIT.

Composition of SEDDS

SEDDS are made of oil and surfactant and rely on three factors: oil–surfactant pair, surfactant concentration, and self-emulsification temperature.

Oils

Oils are the most significant ingredients because they solubilize lipophilic medicines in a particular proportion, allow self-emulsification, and improve intestinal lymphatic system transport and GI tract absorption. SEDDS are made from long-chain and medium-chain triglycerides with various saturations. Corn oil, mono, di, tri-glycerides, olive oil, oleic acid, sesame oil, beeswax, etc. 13-16

Surfactants

SEDDS utilize nonionic surfactants with high hydrophilic–lipophilic balance (HLB) values.17. A stable SEDDS15 requires 30–60% w/w surfactant. Safety makes natural emulsifiers preferable than synthetic ones. Surfactants' high HLB and hydrophilicity help create o/w droplets and distribute the formulation quickly in aqueous medium. Amphophilic surfactants may dissolve or solubilize many hydrophobic medicinal molecules. It prevents medication precipitation in the GI lumen and prolongs drug stability. 18-22

Co-solvents

Effective SEDDS23 requires surfactant concentrations over 30% w/w. Transcutol, propylene glycol, polyethylene glycol, polyoxyethylene, and glycofurol19 may assist dissolve more hydrophilic surfactants or hydrophobic drugs in the lipid base. Some microemulsion systems use these solvents as co-surfactants.

Mechanism of self-emulsification

Reiss states that self-emulsification happens when the energy needed to expand the dispersion's surface area is less than the entropy change that promotes dispersion15. The traditional emulsion's free energy may be expressed by the following equation, which is a direct function of the energy needed to form a new surface between the phases of water and oil:

$$DG = S N_i p r_i 2 S$$

where N, the number of droplets with radii of r and s, represents the interfacial energy, and DG, the process free energy (ignoring the mixing free energy). Emulsifying agents stabilize the emulsion by forming a monolayer on the surface of emulsion droplets, which lowers the interfacial energy and acts as a barrier to prevent coalescence. Over time, the two phases of the emulsion tend to separate and reduce the interfacial area9.

Formulations of SEDDS

The following points should be considered in the formulations of SEDDS

- How soluble medications are in various oils, surfactants, and cosolvents.

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- Choosing oils, surfactants, and cosolvents in accordance with the drug's solubility and phase diagram preparation.
- Using a magnetic stirrer, combine oil, surfactants, and co-surfactant at 500C.
- Next, dissolve the drug in the blank SEDDS while stirring to create an isotropic mixture. This step is crucial because the drug partially disrupts the self-emulsifying process, changing the ideal oil surfactant ratio. Therefore, preformulation solubility and phase diagram studies are needed to design the ideal SEDDS.
- Allowing to come to room temperature and settling for a full day before to use 4.

Preparation of the solid SEDDS6

The basic methods for creating solid SEDDS include solid dispersion, melt extrusion, spray drying, adsorption of solid carriers, and dry emulsion. It is possible to form these solid SEDDS into pellets, pills, and capsules.

Solid carriers

These solid carriers function as self-emulsifying systems (SES) by absorbing liquid or semi-solid formulations. The process is straightforward: SES is mixed with a powder that flows freely and has good adsorption quality23. A blender is used to mix the material until it is evenly adsorbed. Before being compressed into tablets, this solid mixture is either added to additional excipient or put into capsules18. Afterwards, the combination mentioned above may be consolidated into powder forms utilizing a variety of adsorbents, such as silicon dioxide (SylysiaTM 320), magnesium aluminum silicate (NeusilinTMUS2), and microporous calcium silicate (FloriteTM RE).

Spray drying

Using a nozzle22, the created formulation, which includes a medication, solid carrier, oil, and surfactant, is first sprayed into a drying chamber. Tiny solid particles are left behind as the volatile vehicles evaporate. After that, these particles are compacted into tablets or put into capsules.

Melt extrusion

This formulation method relies on the plastic mass material's ability to be readily extruded and pressure-spheronized. Excipient in liquid form need not be added, but it is necessary to maintain a steady temperature and pressure.

Dry emulsion

It is mainly o/w emulsion, which is then converted into solid form by spray drying/solid carrier/ freeze drying.

Melt extrusion/extrusion spheronization

Solvent-free melt extrusion achieves homogeneous composition and 65% drug loading. Extrusion uses a die to drive plastic raw material at a controlled temperature, flow rate, and pressure to generate a product with a uniform size, shape, and density25. The extruder aperture determines the spheroids' approximate size. Pharmaceutical companies utilize extrusion-spheronization to make uniform pellets. Active ingredients and excipients must be combined dry to make a homogeneous powder. To make consistent-sized spheroids, wet massing with a binder must be done before extrusion into a spaghetti-like extrudate. Next, dry sifted and coated (optional) to get the desired size distribution 7.

Capsule filling with liquid and semisolids self emulsifying system3

Capsule filling is the easiest and most usual method for oral liquid or semi-solid SE encapsulation. If used for semisolids, semisolid excipients are heated to at least 2080C (over their melting points), actice compounds are stirred in, and the molten mixture is placed in capsules and cooled to room temperature.

Dosage forms for self emulsifying system

Self emulsifying capsule

Microemulsion droplets develop and spread in the GIT to reach absorption site after capsule administration of traditional liquid SE formulations15. If microemulsion phase separation is permanent, medication absorption won't improve24. This may be solved by adding sodium dodecyl sulfate to SE. A modest amount of HPMC may be used to create and maintain extremely saturatable SEDDS in vivo to avoid medication precipitation. Add solid carriers (absorbents polymers) to liquid SE components to make solid or semi-solid capsules. Consider a solid PEG matrix3.

Self--emulsifying sustained / controlled release tablets

Lipid-surfactant combination is promising for SE tablets. SEDDSs may be gelled to minimize the quantity of solidifying excipients needed to turn them into solid dosage form20. Colloidal silicon dioxide (aerosol 200) may be employed as a gelling agent in oil-based systems to decrease hardening excipients and delay drug release14. SE pills

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provide high side effect protection. Adding indomethacin (or another hydrophobic NSAID) to SE pills may boost GI mucosal membrane penetration and reduce GI hemorrhage. SES generally contains glycerol monolaurate and tyloxapol.

Self emulsifying microspheres

The quasi emulsion solvent diffusion approach for spherical crystallization may produce solid SE sustained release microspheres26. Zedoary turmeric oil release may be regulated by the hydroxypropyl methylcellulose acetate succinate-aerosil 200 ratio29. Oral administration of such microspheres to rabbits results in plasma concentration time profiles with 133.6% bioavailability compared to liquid SEDDS4.

Self emulsifying sustained / controlled release pellets

Pellets have various benefits over solid dosage forms, including flexibility of production, reduced plasma profile variability, and reduced GI discomfort without diminishing drug absorption. SE controlled release pellets with pharmaceuticals in SES increased drug release, although coating with a water-insoluble polymer may lower it. Extrusion/spheronization produces pellets with water-insoluble model pharmaceuticals (methyl and propyl paraben). SES may include polysorbate 803 and mono diglycerides.

Self emulsifying bead

Self-emulsifying system may be solidified with less excipient. Copolymerizing styrene and divinyl benzene produces porous polystyrene beads (PPB) with complicated interior void structures. It is inert and stable at several pH, temperature, and humidity levels. PPB bead size and pore design affect SES-loaded PPB6 loading effectiveness and in vitro drug release.

Self-emulsifying nanoparticles Self-emulsifying nanoparticles may be made using nanoparticle technology. Injectable solvents exist. This approach produces molten lipid mass with lipid, surfactant, and medication. Drops of lipid molten mass are injected into a non-solvent environment. This produces nanoparticles when filtered and dried. This approach yields 100 nm particles with 70-75% drug content. Second, sonication emulsion diffusion evaporation. This approach produced biodegradable PLGA/CMC nanoparticles with 5-flurouracil and antisense EGFR plasmids. No surfactant was needed for the SE action of PLGA and CMC.

Self emulsifying solid dispersion

Solid dispersions may improve water-insoluble medication solubility and bioavailability. These excipients may improve absorption of poorly water-soluble drugs30. Unlike prior PEG solid dispersions, poured straight into firm gelatin capsules in molten state without milling or mixing. Gelucire 44114, labrasol, transcutol, and TPGS (tocopherol / polyethylene glycol 1000 succinate) are commonly used SE excipients3.

Self emulsifying suppositories

S-SEDDS may promote drug GI and rectal/vaginal adsorption24. Oral glycocyrrhizin may reach therapeutic plasma concentrations for chronic hepatic disorders via vaginal or rectal SE suppositories. These formulations included glycyrrhizin and a C6–C18 fatty acid glycerol ester and macrogol ester7.

Self emulsifying implants

SE implant research has substantially improved S-SEDDS. Malignant brain tumors are treated with carmustine, a chemotherapeutic drug. Its short half-life limits its efficacy. Loomis created copolymers with bioresorbable, hydrophilic, and at least two cross-linkable functional groups per polymer chain. These copolymers have SE property without emulsifiers. These copolymers seal implanted prosthesis well.

Table 1. Methods of preparation of SEDDS

Formulation type	Composition	Characteristics
Type I	Oils without Surfactant	Non-dispersible poor solvent capacity except for high lipophilic drugs, requires digestion to releases drug
Type II	Oils and water-insoluble surfactant	SEDDS, turbid o/w dispersion (particle size 0.25-2 µm), unlike to lose solvent capacity on dispersion, possible loss of solvent capacity on digestion

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Type III	Oils, water-soluble surfactants and co-solvents	SEDDS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion, less easily digested, possible loss of solvent capacity on digestion
Type IV	Water-soluble surfactant and co-solvents (oil free)	Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion, unlikely to be digested

Characterization of SEDDS

Visual evaluation is the main self-emulsification test. Self-emulsification efficiency may be determined by measuring emulsification time, droplet size, and turbidity.

Visual assessment

This may provide vital information regarding the mixture's self- and microemulsifying properties and dispersion.9. Measurement of droplets and particles Emulsion droplet sizes are measured by photon correlation spectroscopy using a Zetasizer that can measure 10–4000 nm16. After external standardization using spherical polystyrene beads, light scattering is measured at 25°C at 90°. The particle's nanometric size range is preserved after 100 times water dilution, proving system compatibility with excess water.

Assessment of self emulsification

The USP 24 rotating paddle equipment tests mixture self-emulsification. A spinning paddle at 70 rpm and 37oC gently stirs one gram of mixture into 200 ml of distilled water. Self-emulsification is visually evaluated for rate and emulsion appearance 4.

Viscosity determination

Microemulsion rheology is assessed by Brook Field viscometer if o/w and very viscous if w/o.

Droplet size analysis

Photon correlation spectroscopy with Zeta sizer measures emulsion droplet sizes between 10 and 5000 nm3. Studies of thermodynamic stability A lipid-based formulation's stability affects its performance and may cause drug precipitation in the excipient matrix solution28. Poor physical stability may also cause excipient phase separation, which impacts formulation performance and appearance. Incompatibilities between formulations and gelatin capsule shells may cause brittleness, delayed disintegration, and inadequate medication release. In thermodynamic stability research, three stages are taken.Heating-cooling cycle: At least 48 hours are stored at each of six refrigerator temperatures (50C to 450C). Formulations stable at these temperatures are centrifuged.

Centrifugation: Passed formulations are centrifuged at thaw cycles between 200C and +250C for at least 48 h at 3600 rpm for 20 min. The freeze-thaw stress test uses formulations without phase separation.

Freeze-thaw cycle: Stable formulations demonstrate no phase separation, creaming, or cracking.

Dispersibility test

A standard USP XXII dissolution apparatus 2 dispersibility test evaluates oral emulsion self-emulsification. Add one milliliter of each formulation to 500 mL of water at 37 ± 1 0C. A basic stainless steel dissolving paddle rotates at 50 rpm for mild agitation. Visually grading formulation in vitro performance uses the following approach.:

Grade A: An emulsion that forms rapidly (within one minute) and is transparent or bluish in color.

Grade B: An emulsion that forms rapidly, is marginally less transparent, and exhibits a bluish-white hue.

Grade C: Fine milky emulsion that forming within 2 min.

Grade D: An emulsion that is dull, greyish-white, and faintly oily in appearance, and which emulsifies slowly (for more than two minutes).

Grade E: The formulation displays inadequate or negligible emulsification, as evidenced by the presence of sizable oil globules on the surface.

Grade A and B formulations will remain emulsion-like in GIT. SEDDS formulation 8 may use Grade C formulation. Transmission % and refractive index

The refractive index and % transmittance indicate formulation transparency. A drop of solution on a slide is compared to water (1.222) to calculate the system's refractive index using a refractometer. The UV spectrophotometer measures

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system transmittance at a certain wavelength using distilled water as the blank. Transparent formulations have a refractive index similar to water (1.333) and a transmittance higher than 98%.

In vitro diffusion study

In vitro diffusion experiments use dialysis to evaluate formulation drug release from liquid crystalline phase surrounding droplets3.

Applications

Increased solubility and bioavailability.

Resistance to biodegradation.

SEDDS enable oral administration of hydrophobic medicines.

SEDDS addressed issues with poorly soluble medication delivery.

Examples – SEDDS improves poorly soluble medication bioavailability.

Halofantrine bioavailability is increased with SMEDDS.

Vitamin EBA is three times greater than SEDDS27.

Coenzyme Q10 BA is 2-folds greater than SEDDS.

SEDDS increases progesterone BA-9 folds.

Nimodipine enhanced SMEDDS3 performance in vitro and in vivo..

Recent Approaches in Self Emulsifying Drug Delivery Systems

Surfactant combinations increased plasma profile repeatability for Cmax and Tmax.

Coenzyme Q10 SEDDS improved absorption and lowered toxicity. Triglyceride oil/nonionic SEDDS formed lipophilic molecule WIN 54954.

Simavastin's oral bioavailability has been improved by the development of a self-microemulsifying drug delivery system (SMEDDS). This work showed that SMEDDS could transport hydrophobic compounds10.

A new PTX SEDDS, utilized for solid tumor therapy, demonstrated chemical stability for at least one year in a two-part formulation and boosted drug loading by fivefold. The excipient produced a stable microemulsion with lower cytotoxicity than marketed I.V. formulation15.

The SEDDS and SMEDDS formulation of Halofantrine, an antimalarial medication, improved oral bioavailability by eight times compared to earlier studies.

SMEDDS improved silymarin bioavailability to 1.88.

Using SEDDS, a self-nano emulsified drug delivery system (SNEDDS) for ubiquinone was developed, overcoming typical limitations such limited solubility and irreversible precipitation of the active drug in the medium over time1.

II. FUTURE PROSPECTS

SEDDS and SMEDDS formulations are being converted into powders and granules, which can be processed into conventional 'powder-fill' capsules or compressed into tablets for future formulation development of poorly soluble drugs. Using a waxy solubilising agent as a binding agent, hot melt granulation may add up to 25% solubilising agent to a formulation. The use of inert adsorbents like Neusilin (Fuji Chemicals) and Zeopharm (Huber) to convert liquids into powders for powder fill capsules or tablets is also growing. The ratio of SEDDS to solidifying excipients must be quite high to create solids with adequate processing qualities, which appears impossible for medicines with low oil-phase solubility. Gelling SEDDS would lower the quantity of solidifying excipients needed to convert it into solid dosage forms. Oil-based systems use colloidal silicon dioxide (Aerosil 200) as a gelling agent, which may reduce hardening excipients and delay drug release.

Table No. 2. Some marketed SEDDS products

Drug	Trade Name
Cyclosporine	Neoral
Ritonavir	Norvir
Amphenavir	Agenerase
Sequinavir	Fortovase
Cyclosporine	Gengrafi

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Cyclosporine	Sandimmune

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