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Self-Emulsifying Drug Delivery Systems (SEDDS) For Enhanced Oral Delivery of Lipophilic Drugs

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Abstract:

The oral delivery of hydrophobic drugs presents a major challenge because of the low aqueous solubility of such compounds. Self-emulsifying drug delivery systems (SEDDS), which are isotropic mixtures of oils, surfactants, solvents and co-solvents/surfactants, can be used for the design of formulations in order to improve the oral absorption of highly lipophilic drug compounds. SEDDS can be orally administered in soft or hard gelatin capsules and form fine relatively stable oil-in-water (o/w) emulsions upon aqueous dilution owing to the gentle agitation of the gastrointestinal fluids. The efficiency of oral absorption of the drug compound from the SEDDS depends on many formulation-related parameters, such as surfactant concentration, oil/surfactant ratio, polarity of the emulsion, droplet size and charge, all of which in essence determine the self-emulsification ability. Thus, only very specific pharmaceutical excipient combinations will lead to efficient self-emulsifying systems. Although many studies have been carried out, there are few drug products on the pharmaceutical market formulated as SEDDS confirming the difficulty of formulating hydrophobic drug compounds into such formulations. Significant improvement in the oral bioavailability of these drug compounds has been demonstrated for each case. The fact that almost 40% of the new drug compounds are hydrophobic in nature implies that studies with SEDDS will continue, and more drug compounds formulated as SEDDS will reach the pharmaceutical market in the future.

Keywords: SEDDS, Lipophilic drugs, oral delivery, bioavailability.

Introduction

Emulsions serve as drug carriers in pharmaceutical preparations even though they can likely improve the medicine's oral bioavailability by having poor absorption profiles. The prominent strategies for enhancing the stability of orally administered APIs are to use delivery systems of drugs that are based on lipids. According to the literature, the terminology for lipid-based techniques is highly debated. The initial droplet size is not the primary factor determining micro and nano emulsions (SMEDDS and SNEDDS). If the droplet size of emulsion is in the nanoscale range, the SNEDDS term should be used. SEDDS are oil and surfactant-based preparations with the help of slow agitation that can be emulsified rapidly in water. The chemical structure and physical properties of SEDDS physical qualities were essential determinants of application and tolerance. As a result, these variables must be established at the stage of preformulation.

Advantages

a) Flexibility of dosage forms:

SEDDS can be formulated as liquid or solid forms. Solid forms (solidified SEDDS improve stability, ease of handling, storage, and patient compliance compared to purely liquid systems. Since the dissolution step (which can be rate limiting) is largely bypassed, drug release and absorption tends to be faster.

b) High drug-loading capacity:

Especially for lipophilic drugs, because oils & surfactants can dissolve significant amounts of drug, allowing more drug per dosage form.

c) Targeted absorption / lymphatic transport:

Some SEDDS formulations (especially lipid-based) can promote uptake via the lymphatic system. This has two advantages: bypassing first-pass hepatic metabolism and possibly targeting lymphatic tissues.

d) Ease of manufacture & scalability:

The components (oil, surfactants, co-surfactants) can often be mixed without very complex equipment; also scale up is more straightforward than some more complex nanoparticles or delivery systems.

Formulation Strategies of SEDDS

a) Selection of Excipients:

- **Oil phase**

Solubilizes the lipophilic drug and promotes lymphatic absorption.

Examples: Medium Chain Triglycerides (MCTs), Long Chain Triglycerides (LCTs), ethyl oleate, Captex, Labrafac.

- **Surfactants**

Facilitate self-emulsification and reduce interfacial tension.

Non-ionic surfactants (e.g., Tween 80, Cremophor EL, Labrasol) are most common due to lower toxicity.

- **Co-surfactants / Co-solvents**

Further reduce interfacial tension and improve flexibility of interfacial film.

Examples: Transcutol P, PEG 400, propylene glycol, ethanol.

b) Construction of Pseudo-ternary Phase Diagrams:

Helps determine the optimal ratio of oil, surfactant, and co-surfactant for stable emulsification.

Regions in the diagram show nano-emulsion, micro-emulsion, or phase separation zones.

c) Optimization of Droplet Size:

Goal is smaller droplet size (nano range) for increased surface area and absorption.

High surfactant concentration and proper surfactant/co-surfactant ratios improve droplet size distribution.

d) Drug Incorporation Strategy:

Drug is dissolved in the pre-concentrate (oil + surfactant + co-surfactant mixture).

Heating or sonication may be required for poorly soluble drugs.

Solubility studies of the drug in each component are performed prior to formulation.

Characterization Of SEDDS

a) Visual Assessment / Self-Emulsification Time

Determines how quickly and efficiently the formulation disperses in aqueous medium with mild agitation.

Classified into good (spontaneous, clear emulsion) vs poor (slow, cloudy, phase separation).

b) Droplet Size Analysis & Polydispersity Index (PDI)

Measured using Dynamic Light Scattering (DLS) or Photon Correlation Spectroscopy (PCS).

Smaller droplets (<100 nm for SNEDDS) = higher surface area, better absorption.

PDI < 0.3 indicates uniform droplet distribution.

c) Zeta Potential Measurement

Determines surface charge and stability of the emulsion.

High positive or negative zeta potential → better stability (prevents coalescence).

d) Thermodynamic Stability Studies

Formulations subjected to freeze–thaw cycles, centrifugation, and heating–cooling cycles to ensure no phase separation, cracking, or precipitation.

e) Emulsification Efficiency / Turbidity Measurement

Turbidimetric evaluation using a nephelometer or UV-spectrophotometer.

Lower turbidity = smaller droplet size & better emulsification.

f) Viscosity & Rheological Studies

Carried out with a Brookfield viscometer to assess flow behavior.

Important for capsule filling and prediction of in-vivo performance.

g) Cloud Point Determination

Temperature at which formulation becomes cloudy (due to phase separation of surfactant).

Should be above physiological temperature (37 °C) to ensure stability in vivo.

Therapeutic Applications of SEDDS

a) Enhancing Oral Bioavailability of Lipophilic Drugs

Many BCS class II & IV drugs (low solubility, high permeability) show poor absorption.

SEDDS increase dissolution & absorption.

b) Immunosuppressive Therapy

Used in transplant patients to prevent graft rejection.

Example: Cyclosporine A (Neoral®) & Tacrolimus → SEDDS improve consistent absorption and reduce food effects[19].

c) Anticancer Therapy

Many anticancer drugs are highly lipophilic with poor bioavailability.

Examples:

1. Paclitaxel (solubility enhancement with SNEDDS).
2. Tamoxifen (breast cancer therapy).

Future Perspectives of SEDDS

a) Solid SEDDS (S-SEDDS) Development

Transforming liquid SEDDS into solid dosage forms (tablets, pellets, capsules) improves Stability, handling, storage, and patient compliance.

Techniques: adsorption on carriers, spray-drying, melt granulation, extrusion.

b) Supersaturated SEDDS (S-SEDDS)

Incorporation of precipitation inhibitors (e.g., polymers like HPMC, PVP) to prevent drug crystallization after dilution in GI fluids.

Ensures higher and sustained drug concentrations for absorption.

c) Targeted & Site-Specific Delivery

Modification of SEDDS with mucoadhesive polymers, ligands, or nanoparticles can allow targeting of specific tissues (e.g., lymphatic targeting, brain delivery).

Useful in cancer therapy, CNS disorders, and immunotherapy.

d) Parenteral and Alternative Routes

Exploration of SEDDS for parenteral, ocular, transdermal, and pulmonary delivery.

Example: Nanoemulsifying eye drops for poorly soluble drugs (e.g., cyclosporine for dry eye).

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