

LIPID-BASED CARRIERS IN DRUG DELIVERY: SPOTLIGHT ON SELF-EMULSIFYING SYSTEMS**Diksha Sahu, Reena Shende*, Satkar Prasad, Shailesh Kumar Ghatuway****RKDF School of Pharmaceutical Sciences, BHABHA University, Bhopal (M.P.)***Corresponding Author's E mail: emi.89ryadav@gmail.com

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ABSTRACT

One promising strategy for improving the oral bioavailability of medications that are not very water soluble is the use of self-emulsifying drug delivery systems, or SEDDS. SEDDS increase drug solubilization, absorption, and overall therapeutic efficacy by forming fine oil-in-water emulsions when the gastrointestinal tract is mildly agitated. These systems reduce first-pass metabolism by facilitating lymphatic transport and avoiding the dissolution step, which is frequently a rate-limiting factor in oral drug delivery. For stable emulsification and drug loading, formulation ingredients like oils, surfactants, and co-surfactants are essential. For increased stability, patient compliance, and commercial viability, SEDDS can be further optimized in solid dosage forms (such as tablets and capsules). In conclusion, SEDDS present a flexible and effective delivery system for hydrophobic medications and have a great deal of promise for further pharmaceutical advancement. Therefore, the present review work has been done to give an insight of lipid-based carriers in self-emulsifying systems.

Keywords: SEDDS; Emulsification; Self emulsification; Solubility; Enhancement.

INTRODUCTION

The oral route of drug administration is considered the most convenient and widely accepted approach due to its non-invasive nature, patient compliance, and cost effectiveness. However, it presents substantial challenges for drug molecules with poor aqueous solubility, as the initial step for effective absorption is dissolution in the gastrointestinal (GI) tract¹. A significant proportion, nearly 40% of new chemical entities, exhibit low water solubility, which lead to the limited and variable oral bioavailability, making this a major hurdle in modern drug delivery system development². For drugs classified under **Biopharmaceutical Classification System (BCS) Class II**, which are characterized by low solubility and high permeability, solubilization within the GI tract becomes the rate-limiting step for absorption². Traditional approaches to improve solubility such as micronization, solid

dispersion, and cyclodextrin complexation have been explored. However, while these methods offer some benefits, they are often associated with limited success or undesirable drawbacks such as poor stability, scalability issues, or complex processing requirements². Self-emulsifying drug delivery systems (SED DS) have emerged as a promising strategy to overcome solubility limitations and enhance the bioavailability of poorly water-soluble drugs. SED DS are isotropic mixtures of oils and surfactants, often incorporating co-solvents that spontaneously form fine oil-in-water emulsions upon contact with aqueous fluids under gentle agitation, such as that provided by gastric motility. These systems are typically encapsulated in hard or soft gelatin capsules for oral administration, and upon aqueous dilution in the GI tract, they form stable emulsions facilitating efficient drug dispersion³. The efficiency of SED DS lies in their ability to present the drug in a solubilized form, along with their capacity to generate small emulsion droplet sizes, which increase the surface area available for absorption. Typically, SED DS produce emulsions with droplet sizes in the range of 100–300 nm, while **Self-Microemulsifying Drug Delivery Systems (SMED DS)** generate transparent microemulsions with droplet sizes below 50 nm. Compared to conventional emulsions, which are often metastable and sensitive to storage conditions, SED DS are more physically stable and easier to manufacture⁴. The process of self-emulsification involves the formation of intermediate structures, such as liquid crystals and gel phases, at the oil-water interface. These liquid crystalline phases play a critical role in drug release, as they influence the droplet curvature and the resistance to drug diffusion into the aqueous phase⁵. Therefore, the formation and structure of these interfacial phases directly impact the release profile and bioavailability of the drug.

Need for Self-Emulsifying Drug Delivery Systems (SED DS)

Self-emulsifying drug delivery systems (SED DS) have gained prominence as an effective oral delivery approach for poorly water-soluble drugs. By pre-dissolving hydrophobic drug molecules in a lipidic or surfactant-based vehicle and encapsulating them in a dosage form such as soft or hard gelatin capsules, the initial dissolution step in the gastrointestinal (GI) tract can be bypassed, thereby enhancing absorption. The principal advantage of SED DS lies in overcoming the rate-limiting step of drug dissolution by maintaining the drug in a solubilized state before reaching the site of absorption. However, one of the potential challenges associated with SED DS is drug precipitation upon dilution in the GI tract, especially when hydrophilic solvents (e.g., polyethylene glycol) are used. This is due to the unfavorable thermodynamic environment leading to drug supersaturation and subsequent precipitation. When lipophilic vehicles are employed instead, the likelihood of precipitation is

reduced since the partitioning kinetics favors retention of the drug within the lipid droplets even after aqueous dilution⁶.

Advantages of SEDDS

SEDDS offer several pharmacokinetic and formulation-related benefits that make them a preferred choice for the delivery of lipophilic drug molecules. These include⁷:

1. Protection of sensitive drug substances from hydrolytic or enzymatic degradation
2. More consistent and predictable drug absorption
3. Site-specific targeting within the gastrointestinal tract
4. Reduced exposure of drugs to the harsh GI environment
5. Controlled and sustained release profiles
6. Minimization of food-effect variability
7. Enhanced oral bioavailability, enabling dose reduction
8. High drug loading potential
9. Applicability to both liquid and solid dosage forms

Key Components of SEDDS

The efficiency of the self-emulsification process is influenced by several formulation parameters, including the type and concentration of oil and surfactant, as well as the temperature at which emulsification occurs⁸.

Oils

Oils serve as the primary excipient in SEDDS formulations. They provide a solubilizing medium for lipophilic drugs and play a significant role in promoting intestinal lymphatic transport, thereby improving systemic absorption¹⁰. Both long-chain triglycerides (LCTs) and medium-chain triglycerides (MCTs), with varying saturation levels, are commonly used. Among these, modified or hydrolyzed vegetable and edible oils have shown substantial success due to their compatibility and physiological advantages⁹. Furthermore, novel semisynthetic MCTs possessing intrinsic surfactant-like properties have largely replaced conventional MCTs in many modern formulations¹⁰.

Surfactants

Surfactants are crucial for emulsification, particularly non-ionic types with high hydrophilic–lipophilic balance (HLB) values. Commonly used surfactants include Tween, Labrasol, Labrafac CM 10, and

Cremophor. These agents facilitate the spontaneous formation of fine oil-in-water emulsions upon dilution and contribute to the physical stability of the system. Natural-source surfactants are generally considered safer than synthetic analogues. The surfactant concentration typically ranges from 30% to 60% w/w, sufficient to ensure emulsification. However, excessive surfactant use can cause gastrointestinal irritation, though non-ionic surfactants are known to exhibit lower toxicity compared to their ionic counterparts. The amphiphilic nature of surfactants allows them to dissolve or solubilize considerable amounts of hydrophobic drugs. This not only prevents precipitation within the GI lumen but also maintains drug solubility for prolonged periods, thereby enhancing absorption¹¹.

Co-solvents

Co-solvents are often incorporated into SEDDS formulations to enhance the solubility of surfactants and hydrophobic drugs. Examples include ethanol, propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, and tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofuro). These agents can also function as co-surfactants, improving microemulsion stability. Despite the usefulness of alcohol-based co-solvents, alcohol-free self-emulsifying systems have been reported, expanding the formulation possibilities¹².

Formulation of SEDDS:

Formulation Considerations for SEDDS

A wide range of excipients such as oils, biological lipids, hydrophobic and hydrophilic surfactants, and water-soluble co-solvents are available for the development of self-emulsifying drug delivery systems (SEDDS). These excipients can be strategically combined to produce formulations suitable for encapsulation into soft or hard gelatin capsules or as mixtures that spontaneously form fine colloidal emulsions upon aqueous dispersion¹³.

The formulation of an effective SEDDS should take into account several critical parameters:

- The solubility of the drug in various oils, surfactants, and co-solvents
- Selection of excipients based on solubility data and the construction of a ternary phase diagram¹⁴
- The actual process of formulation, which involves dissolving the drug into a blend of oil, surfactant, and co-solvent

The incorporation of the active pharmaceutical ingredient (API) into a SEDDS can influence the self-emulsification behaviour by altering the optimal oil-to-surfactant ratio. Therefore, designing an optimal formulation requires thorough preformulation studies, including solubility screening and phase diagram construction. For the development of prolonged-release SEDDS, additional excipients such as polymers or gelling agents may be included to modulate drug release kinetics¹⁵.

Mechanism of Self-Emulsification

Although the exact mechanism of self-emulsification is not fully understood, it has been proposed most notably by Reiss that emulsification occurs when the entropy change favoring dispersion exceeds the energy required to expand the surface area between phases. The free energy of a conventional emulsion is governed by the interfacial energy. Over time, emulsions tend to phase-separate to reduce interfacial energy, unless stabilized by emulsifying agents that form protective monolayers around droplets, reducing surface tension and preventing coalescence¹⁶. In SEDDS, emulsification typically requires very little external energy. This is possible when interfacial structures are destabilized through local surface shear, allowing spontaneous droplet formation. For such spontaneous emulsification to occur, the interfacial layer must offer no resistance to shear stress. When the free energy required for emulsion formation is negligible or negative, the process occurs automatically without mechanical input¹⁷.

Evaluation of SEDDS

1. Thermodynamic Stability Studies

Physical stability is crucial for the performance of lipid-based formulations. Instabilities such as phase separation or drug precipitation can compromise bioavailability and aesthetic quality. Incompatibilities with the gelatin capsule shell may further lead to shell brittleness, delayed disintegration, or incomplete drug release.

Thermodynamic stability of SEDDS is typically assessed through three steps:

- **Heating–Cooling Cycle:** Formulations are subjected to six temperature cycles between 4°C and 45°C, with each temperature maintained for at least 48 hours. Stable formulations proceed to the next step.
- **Centrifugation Test:** The passed formulations are centrifuged at 3500 rpm for 30 minutes. Those that do not exhibit phase separation advance to freeze–thaw testing.

- **Freeze–Thaw Cycle:** This involves three freeze–thaw cycles between -21°C and $+25^{\circ}\text{C}$, each held for a minimum of 48 hours. Formulations that pass this stage demonstrate robust physical stability without signs of phase separation, creaming, or cracking¹⁸.

2. Dispersibility Test

The ability of SEDDS to spontaneously emulsify is evaluated using the USP XXII dissolution apparatus 2. One milliliter of the formulation is added to 500 mL of water maintained at $37 \pm 1^{\circ}\text{C}$. A standard stainlesssteel paddle is rotated at 50 rpm to simulate mild agitation. The emulsification behavior is then visually assessed and graded:

- **Grade A:** Rapid (within 1 minute) formation of a clear or slightly bluish nanoemulsion
- **Grade B:** Rapid formation of a slightly less clear bluish-white emulsion
- **Grade C:** Fine milky emulsion formed within 2 minutes
- **Grade D:** Greyish-white emulsion with slightly oily appearance; emulsification takes longer than 2 minutes¹⁸.

Advanced Evaluation Techniques for SEDD

Emulsification Grading

Formulations that exhibit minimal emulsification with large oil globules remaining on the surface may indicate suboptimal performance. Among the dispersibility grades, **Grade A** and **Grade B** formulations typically maintain nanoemulsion characteristics upon dispersion in the gastrointestinal tract, thus demonstrating superior emulsification. In contrast, **Grade C** emulsions, though slightly less efficient, are still considered acceptable for the formulation of SEDDS¹⁸.

Turbidimetric Evaluation

Nepheloturbidimetric analysis is employed to monitor the emulsification process by assessing the increase in turbidity. A fixed volume of the self-emulsifying system is added to a specified quantity of aqueous medium (e.g., 0.1N hydrochloric acid), stirred continuously at 50 rpm on a magnetic stirrer with heating capabilities. The resultant turbidity increase is recorded using a turbidimeter. However, because emulsification often occurs rapidly, monitoring the real-time rate of turbidity change can be technically challenging^{19,20}.

Viscosity Determination

Given that SEDDS are typically administered in soft or hard gelatin capsules, their viscosity must be appropriate for ease of encapsulation. Excessive viscosity may hinder dosing and capsule filling.

Rheological properties are analyzed using instruments such as the Brookfield viscometer. Viscosity measurements can also help determine the emulsion type: low-viscosity formulations generally indicate an oil-in-water (o/w) system, while high-viscosity systems may suggest water-in-oil (w/o) characteristics^{19,20}.

Droplet Size and Particle Size Analysis

Droplet size significantly influences the rate and extent of drug absorption. It is typically measured by photon correlation spectroscopy (PCS), which quantifies fluctuations in light scattering caused by the Brownian motion of droplets. Measurements are conducted using instruments such as the Zetasizer, capable of analyzing particle sizes ranging from 10 to 5000 nm. Light scattering is typically recorded at 25°C at a 90° angle. Notably, the nanometric droplet size remains consistent even after 100-fold dilution, indicating strong formulation stability in excess aqueous environments^{19,20}.

Refractive Index and Percent Transmittance

These parameters are indicators of formulation clarity and transparency. The refractive index is measured by applying a drop of the sample to a refractometer slide and comparing it against the standard value for water (1.333). Percent transmittance is determined using a UV-visible spectrophotometer, with distilled water as the blank. Formulations demonstrating a refractive index close to water and transmittance values above 99% are considered optically transparent.

Electroconductivity Studies

The electroconductivity of the SEDDS formulation is measured to assess the presence of ionic species and determine system type. SEDDS generally consist of surfactants (ionic or non-ionic), oil, and water. The charge on oil droplets in conventional SEDDS is typically negative, attributed to free fatty acids. Conductivity measurements are carried out using an electro conductometer, and results can offer insights into the system's structure and potential droplet interactions²¹.

In Vitro Diffusion Study

Drug release from SEDDS is evaluated through in vitro diffusion studies, typically employing dialysis techniques. These tests aim to assess the diffusion behavior of the drug from the liquid crystalline

interfacial layer surrounding the emulsion droplets. The release profile offers insights into how the drug may behave once administered¹⁹.

Drug Content Analysis

Drug loading in the SEDDS is determined by dissolving a known quantity of the formulation in an appropriate solvent. The extracted drug is then quantified using validated analytical techniques, compared against a standard calibration curve. This ensures uniformity and accuracy of drug dosing in the final product⁷.

Critical Factors Affecting SEDDS Performance

Polarity of the Lipophilic Phase

The polarity of the lipid phase is a major determinant of drug release rate from SEDDS. Parameters such as the hydrophilic–lipophilic balance (HLB), fatty acid chain length, degree of saturation, emulsifier concentration, and molecular structure influence the droplet's polarity. Increased polarity facilitates a faster drug release into the aqueous environment. For instance, studies by Sang-Cheol Chi have shown that the release rate of idebenone was higher when formulated with oils possessing greater polarity²⁷.

Nature and Dose of the Drug

Drugs requiring high therapeutic doses may not be ideal candidates for SEDDS unless they exhibit exceptional solubility in at least one formulation component—preferably the lipid phase. Poor solubility in both aqueous and lipid phases poses significant formulation challenges. The ability of a SEDDS to maintain a drug in a solubilized state depends on its oil solubility. If surfactants or co-surfactants play a major role in solubilization, the dilution of the system *in vivo* could lower the solvent capacity and trigger drug precipitation. Equilibrium solubility studies are critical for anticipating precipitation risks. However, crystallization kinetics is typically slow in solubilizing environments, providing a transient window for absorption²⁷. Studies, such as those by Pouton, have highlighted the extended equilibration time required for certain lipid-based formulations—up to five days in some cases. Furthermore, it was observed that a drug can remain in a supersaturated state for up to 24 hours post-emulsification. This finding suggests that precipitation within the gastrointestinal tract may not occur before absorption takes place. In fact, maintaining a supersaturated state enhances the thermodynamic activity of the drug, potentially improving absorption rates. These observations

underscore the need for predictive in vitro models to evaluate the in vivo behavior of lipid-based drug delivery systems following dispersion in the gastrointestinal environment.

Drawbacks of SEDDS

Despite their numerous advantages, self-emulsifying drug delivery systems (SEDDS) face limitations, primarily due to the absence of reliable in vitro assessment models. Traditional dissolution techniques are not suitable for evaluating these systems, as their drug release often depends on enzymatic digestion within the GI tract. To address this, in vitro simulation models mimicking duodenal digestion have been introduced. However, these systems require further refinement and validation to enhance their predictive value. Progress in this area will rely on the establishment of in vitro–in vivo correlations and the use of suitable animal models to evaluate different prototype lipid-based formulations⁷.

Applications of SEDDS

1. Improvement in Solubility and Bioavailability

SEDDS are particularly effective in improving the solubility and bioavailability of poorly water-soluble drugs, especially BCS Class II compounds that exhibit high permeability but low solubility. By bypassing the dissolution step, SEDDS enable more efficient drug absorption. A notable example is **ketoprofen**, a moderately lipophilic non-steroidal anti-inflammatory drug (NSAID) that has been challenging to formulate for sustained release due to its low solubility and associated gastric irritation. Although various approaches—such as nano-crystalline formulations, matrix pellets²², microparticles²³, floating oral systems²⁴, and transdermal patches²⁵ have been employed to improve ketoprofen delivery, each comes with technical or economic limitations. In contrast, formulating ketoprofen in a SEDDS matrix has demonstrated enhanced bioavailability due to improved solubilization. Additionally, the incorporation of gelling agents within the SEDDS has shown promise in achieving sustained release. Upon administration, the lipid matrix in the SEDDS readily forms an oil-in-water (o/w) emulsion, allowing the drug to remain dissolved and increasing its exposure to the intestinal mucosa, which leads to improved systemic absorption. This is typically reflected in increased **C_{max}** and **AUC** values. These drugs are listed in **Table 1**.

Table 1: Examples of Bioavailability Enhancement of Poorly Soluble Drugs Using SEDDS and SMEDDS Formulations

Sr. No.	Compound	Observation After Study	Reference
1	Halofantrine	Trend to higher bioavailability (BA) from long-chain triglyceride (LCT) SMEDDS	10
2	Ontazolast	BA increase of at least 10-fold from all lipid-based formulations	32
3	Vitamin E	BA 3-fold higher from SEDDS	28
4	Coenzyme Q10	BA 2-fold higher from SEDDS	29
5	Progesterone	BA 9-fold higher from SEDDS	30
6	Tocotrienols	BA 2–3-fold higher from SEDDS	31
7	Silymarin	BA approximately 2- to 50-fold higher from SMEDDS	33

2. Protection against biodegradation

SEDDS also offer protective advantages for labile drug molecules that are prone to degradation in the gastrointestinal tract due to acidic pH, enzymatic activity, or hydrolytic breakdown. The lipid matrix and liquid crystalline interface in SEDDS can act as a protective barrier, shielding the drug from direct exposure to degradative conditions. This dual role of protecting the drug, while enhancing its absorption is particularly beneficial for compounds with poor solubility and stability.

CONCLUSION

Self-emulsifying drug delivery systems represent a robust platform for the oral administration of hydrophobic and poorly soluble drugs. By enhancing solubility, promoting absorption, and offering protection against gastrointestinal degradation, SEDDS have demonstrated a significant improvement in the oral bioavailability of challenging drug candidates. Continued research and refinement of in vitro

models will further expand their applicability in modern pharmaceutical formulations. As such, SEDDS hold great promise for advancing oral drug delivery and overcoming current limitations in the formulation of poorly water-soluble therapeutics.

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