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Self-Emulsifying Drug Delivery System – a New Approach to Enhance Oral Delivery

Mr.S.Sinthan[1*] , Mrs.K.Malarvizhi[2]

[1]Department of Pharmaceutics, Pallavan Pharmacy College, Kanchipuram – 631 502

[2]M.Pharm , Assistant professor, Department of Pharmaceutics, Pallavan Pharmacy College, Kanchipuram- 631 502

ABSTRACT:

Self-emulsifying drug delivery systems (SEDDS) have emerged as a promising solution to overcome the limitations of oral drug delivery for hydrophobic drugs. These systems create fine oil droplets or micelle dispersions in gastrointestinal fluids, enhancing drug absorption and bioavailability. SEDDS are composed of natural or synthetic oils, surfactants, and co-solvents, which form a stable emulsion when diluted in water. The mechanism of self-emulsification is not fully understood, but it is influenced by the entropy of the system and the formation of a liquid crystal phase at the droplet surface. SEDDS offer several advantages, including improved solubility, enhanced absorption, ease of manufacture, and consistent results. However, they also have limitations, such as the need for high surfactant concentrations, potential gastrointestinal irritation, and chemical instability of drugs. The development of SEDDS involves a systematic approach, including the preparation of the lipid phase, mixing with surfactants, and optimization using phase diagrams. Characterization of SEDDS involves visual observation, droplet size analysis, zeta potential measurement, emulsification time, cloud point determination, viscosity measurements, liquefaction time, and nuclear magnetic resonance studies. SEDDS have a wide range of applications in the pharmaceutical field, including improved bioavailability, oral drug delivery, reduction of gastric irritation, targeted drug delivery, and versatility in dosage forms. This review provides an overview of the principles, components, advantages, limitations, and applications of SEDDS, highlighting their potential to overcome challenges associated with poorly soluble drugs.

KEYWORDS: SEDDS, Hydrophobic drugs, Droplet, Bioavailability, Oral drug delivery.

1. INTRODUCTION:

In the history of drug discovery, nearly half of the drugs are formulated as Oral delivery. Amongst those, most of the drug's action is hindered due to their high hydrophobicity nature and enzymatic and absorption limitations of GI tract. Even though the drug is more vital and produce very important action, selection of delivery system is mandatory. Most of the oral drug delivery system possess poor bioavailability. To overcome these issues, various strategies has been exploited for the formulation, such as use of Surfactant, lipids, permeation enhancer, salt formulation, micronisation, nano particles etc. The SEDDS for the past few years has risen as interest in the lipid and protein oral administrations. Emulsions are known for its improved bioavailability by having poor absorption rate. But they also resulted in their own set of complexities, such as manufacturing problems and stability issue. Thus, an attention was seeked towards Self-emulsifying drug delivery system which has overcome most of the issues faced by the Oral delivery systems.

2. SELF-EMULSIFYING DRUG DELIVERY SYSTEM (SEDDS):

Self-Emulsifying drug delivery systems (SEDDS) or Self-emulsifying oil formulations (SEOF) are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants. When these systems are gently shaken and then diluted in aqueous media such as GI fluids, they form a fine o/w emulsion or microemulsion (SMEDDS). Typically, SMEDDS can produce transparent microemulsion with a droplet size of 50nm, whereas SEDDS form emulsion with a droplet size of 100nm to 300nm.In contrast to emulsions, SEDDS are easily manufactured and physically stable. Thus, these methods may provide an enhancement in the rate and extent of absorption and lead to more repeatable blood-time profiles for lipophilic drugs, which has a low dissolution rate limited absorption.

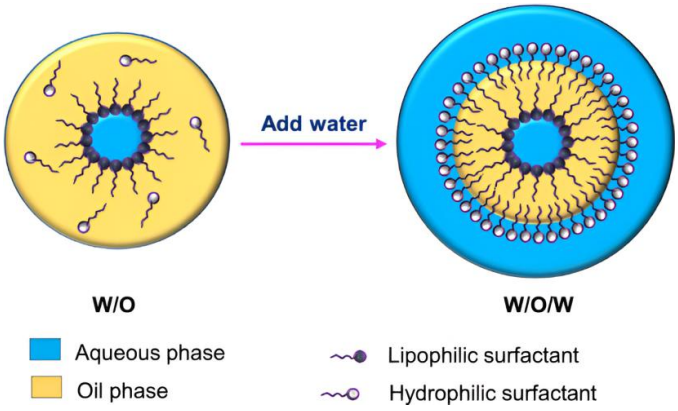

Figure 1: SEDDS

3. COMPONENTS OF SEDDS:

3.1. Oil:

The oil is an essential excipient in SEDDS formulations as it can solubilize lipophilic drugs and aid in self-emulsification. Additionally, it can increase the fraction of lipophilic drugs transported via the intestinal lymphatic system, leading to increased absorption from the GI tract based on the triglyceride's molecular structure. Edible oils are less favored for SEDDS due to their limited ability to dissolve lipophilic drugs. Instead, modified or hydrolyzed vegetable oils are commonly used as they enhance emulsification, improve drug solubility, and mimic intestinal digestion products. Novel semi-synthetic medium-chain derivatives with surfactant properties are increasingly replacing regular medium-chain triglycerides in SEOFs due to their effectiveness.

3.2. Surfactant:

Non-ionic surfactants with high hydrophilic-lipophilic balance (HLB) are ideal for designing self-emulsifying systems (SEDDS), with common emulsifiers like ethoxylated polyglycolyzed glycerides and Tween 80. Natural emulsifiers are safer but less effective at self-emulsification. While non-ionic surfactants are less toxic than ionic ones, they may temporarily affect intestinal permeability. Surfactant concentrations typically range from 30–60% w/w to ensure stability, but excessive amounts can cause gastrointestinal irritation. Safety and proper concentration are key. Surfactants with high HLB and hydrophilicity in SEDDS enable rapid formation of o/w droplets, enhancing absorption by preventing drug precipitation and maintaining solubility. Amphiphilic surfactants dissolve hydrophobic drugs, and higher surfactant-to-oil ratios produce SMEDDS. Droplet size is influenced by surfactant concentration—higher concentrations can either stabilize or disrupt oil-water interfaces, depending on the formulation. A study on paclitaxel SEDDS with tyloxapol/sodium deoxycholate achieved fivefold higher drug incorporation and masked cytotoxicity, likely due to surfactant localization at the oil-water interface near cell membranes.

3.3. Cosolvents / Coemulsifiers:

To produce effective SEDDS, surfactants are needed at concentrations above 30% w/w. Organic solvents like ethanol, PG, and PEG aid in dissolving hydrophilic surfactants or drugs in the lipid base and can function as co-surfactants in microemulsions. However, volatile co-solvents may evaporate, causing drug precipitation in gelatin capsules, which led to the development of alcohol-free formulations with limited ability to dissolve lipophilic drugs.

4. Mechanism Of Action of SEDDS:

The mechanism behind self-emulsification is not fully understood. It is suggested that self-emulsification occurs when the entropy promoting dispersion outweighs the energy needed to increase the dispersion's surface area. In conventional emulsions, free energy is tied to the energy required to create a surface between oil and water, and phases tend to separate over time to lower interfacial area and energy. Emulsifiers in traditional systems stabilize the emulsion by forming a monolayer around droplets, reducing interfacial energy and preventing coalescence.

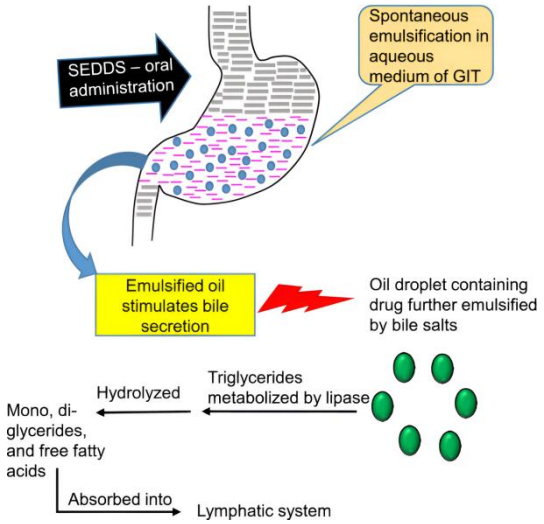

Figure 2: MOA of SEDDS

In contrast, SEDDS emulsify spontaneously because the free energy needed for emulsion formation is either very low, positive, or negative. A lack of resistance in the interfacial structure to surface shearing is essential for emulsification. The ease of emulsification is linked to water penetration into liquid crystal (LC) or gel phases at the droplet surface. When a binary mixture of oil and non-ionic surfactant is added to water, an interface between the oil and water forms, leading to water solubilization in the oil phase. As the solubilization limit is reached, further water penetration creates a dispersed LC phase around the interface. Gentle agitation allows water to quickly infiltrate the aqueous cores, disrupting the interface and forming droplets. The LC phase stabilizes the oil droplets, making SEDDS highly resistant to coalescence.

Studies, including particle size analysis and low-frequency dielectric spectroscopy (LFDS), suggest a complex link between LC formation and emulsion formation. The drug compound in the formulation may influence emulsion characteristics through interactions with the LC phase, though the exact relationship between LC formation and spontaneous emulsification remains unproven.

5.Factors affecting SEDDS:

5.1.Dose and nature of drug:

SMEDDS are generally unsuitable for administering drugs at very high doses unless the drug exhibits significant solubility in at least one of the formulation components, particularly within the lipophilic phase. A key challenge arises when dealing with drugs that have poor solubility in both aqueous and lipid environments, typically characterized by low log P values. This inherent solubility limitation poses considerable difficulties in formulating such drugs within SMEDDS.

5.2.Polarity of the lipophilic phase:

The release of a drug from microemulsions is influenced by factors such as the polarity of the lipid matrix. Parameters like the HLB value, chain length, degree of fatty acid unsaturation, and the molecular weight of micronized components affect droplet polarity. These factors play a crucial role in preventing crystallization and maintaining the drug's supersaturated state for an extended period.

6. Advantages:

Self-emulsifying drug delivery systems (SEDDS) come with some fantastic benefits:

1. **Better Solubility**: They’re great for making drugs that don’t mix well with water more soluble, which means they can work more effectively.
2. **Improved Absorption**: SEDDS help the body absorb drugs better, increasing their overall effectiveness.
3. **Easy to Make**: These systems are relatively simple to manufacture and tend to stay stable over time.
4. **Consistent Results**: They reduce the ups and downs in how drugs are absorbed by different people or even the same person at different times.
5. **Avoiding First-Pass Metabolism**: SEDDS can deliver drugs directly into the lymphatic system, helping bypass the liver’s metabolism and making the drugs more potent.
6. **Adaptable**: They can be tailored to suit a variety of drugs and are especially helpful for oral medication.

In short, SEDDS make it easier to unlock the full potential of tricky-to-use drugs while being flexible and user-friendly!

7. Limitations:

One challenge in developing SEDDS and other lipid-based formulations is the lack of reliable in vitro models for predicting their behavior. Traditional dissolution methods are inadequate since these formulations often rely on gut digestion before releasing the drug. A model simulating duodenal digestion has been created but requires further refinement and validation before its effectiveness can be established. Additionally, the development process depends on in vitro–in vivo correlations, requiring the creation and testing of multiple prototype formulations in suitable animal models.
Other issues include the chemical instability of drugs and the high surfactant concentrations (30–60%) in formulations, which may irritate the gastrointestinal tract (GIT). Volatile co-solvents in conventional self-microemulsifying formulations can also diffuse into gelatin capsule shells, leading to drug precipitation. The dilution of hydrophilic solvents may further increase the tendency for drugs to precipitate. Moreover, validating complex formulations with multiple components adds another layer of difficulty.

8. FORMULATION OF SEDDS:

Step 1: Preparation of the Lipid Phase:

The oil serves as a carrier for the drug. Heating it to 40°C–60°C helps ensure better solubilization of the drug, especially for compounds with low solubility at room temperature.

Stirring the oil-drug mixture continuously until the drug is completely dissolved is critical. It's essential to verify that no drug precipitate remains visible before moving to the next step.

Step 2: Mixing with Surfactants:

Gradually add the surfactants and co-surfactants to the drug-oil mixture while stirring to avoid phase separation.

Using a homogenizer ensures uniform distribution and forms a homogeneous, isotropic system. The clear, single-phase nature of the mixture indicates proper blending.

Step 3: Optimization Using Phase Diagrams:

Phase diagrams are constructed by plotting various ratios of oil, surfactant, and co-surfactant. These diagrams help identify the optimal range where self-emulsification is most effective.

Testing these ratios involves observing the emulsification behavior of the mixture when it comes into contact with aqueous media, like gastrointestinal fluids.

8.1. Drug incorporation into SEDDS:

Low aqueous solubility drugs are difficult to formulate because they are highly hydrophobic and cannot dissolve in the majority of authorized solvents. Generally speaking, new synthetic hydrophilic oils and surfactants dissolve hydrophobic medications more readily than traditional vegetable oils. Increased drug solubility in the lipid vehicle may also result from the addition of solvents like ethanol, PG, and PEG. Drug/system physicochemical compatibility determines how well a drug is incorporated into a SEDDS, which is typically case-specific. A change in the ideal oil/surfactant ratio is typically the result of the medicine interfering somewhat with the self-emulsification process. The effectiveness of a SEDDS can be influenced by the drug compound's interaction with the mixture's components, either through contact with the liquid crystalline (LC) phase or by penetrating the surfactant interfacial monolayer. Such interactions might disrupt the self-emulsification process, leading to variations in droplet size distribution that depend on drug concentration. It is important to note that incorporating the drug is more likely to cause changes in emulsions with smaller oil droplets, especially in more complex formulations. Thus, conducting pre-formulation solubility tests and phase diagram studies is crucial to designing an optimal SEDDS.

9. CHARACTERISATION OF SEDDS:

9.1.Visual observation:

Visual observation plays a vital role in assessing self-emulsification. When SEDDS is diluted with water, the formation of a clear, transparent, and isotropic solution indicates the creation of a microemulsion. On the other hand, an opaque, milky-white appearance suggests the evolution of a macroemulsion. The stability of the formulation is confirmed if there’s no sign of precipitation or phase separation.

9.2. Analysis of Droplet size:

The size of the droplets in a formulation depends on the type and amount of surfactant used. When SMEDDS is mixed with water, it creates a microemulsion with a consistent and uniform droplet size. This precise distribution is crucial for effective drug release, better absorption within the body, and maintaining the stability of the formulation. To measure droplet size, advanced techniques like Dynamic Light Scattering (DLS) are used.

9.3. Zeta potential measurement:

Zeta potential represents the stability of an emulsion after dilution. A higher zeta potential offers improved stability of the formulation. Compared to particles with a single surface charge, particles possessing a zwitter ion charge show enhanced biocompatibility and remain in the bloodstream for a longer duration.

9.4. Emulsification time:

The time required for a formulation to emulsify depends on the oil-to-surfactant ratio and the composition of the oil phase. This is measured using basket dissolution equipment, which monitors the formation of a clear solution as the formulation is gradually added, drop by drop, into an agitated, water-filled basket.

9.5. Cloud point determination:

The cloud point of a homogeneous solution refers to the temperature at which the solution becomes cloudy and loses its transparency. At temperatures above the cloud point, surfactants typically lose their micelle-forming capability. This point is identified by gradually increasing the temperature of the formulation and measuring turbidity using a spectrophotometer. The cloud point corresponds to the temperature where a drop in percentage transmittance is observed. For effective self-emulsification, formulations should have a cloud point exceeding 37.5°C.

9.6. Viscosity measurements:

The viscosity of diluted SMEDDS formulations, classified as microemulsions, is assessed using precision instruments such as a rheometer or a Brookfield viscometer. These devices employ a cone-and-plate configuration with a rotating spindle to ensure accurate viscosity measurements, facilitating the evaluation and optimization of the formulation's properties.

9.7. Liquefaction time:

This analysis evaluates the time required for S-SEDDS to dissolve in a stationary simulated gastrointestinal (GI) environment. The dosage form is attached to the bulb of a thermometer and wrapped in transparent polyethylene film. The thermometer is then immersed in 250 mL of simulated gastric juice (without pepsin) contained in a round-bottom flask, maintained at 37°C. The liquefaction time is recorded once the dosage form fully melts.

9.8. Nuclear magnetic resonance (NMR) studies:

These techniques are employed to investigate the structural dynamics and behavior of microemulsions. Self-diffusion assessments, often utilizing tracer methods such as radio labeling, provide detailed insights into the mobility and microenvironment of individual components. The Fourier Transform Pulsed-Gradient Spin-Echo (FTPGSE) method applies magnetic gradients to the samples, allowing for rapid and simultaneous measurement of self-diffusion coefficients across multiple components. The calculation of these coefficients is facilitated using the Stokes–Einstein equation, ensuring a precise understanding of the factors influencing self-diffusion within microemulsions.

$$D = KT/6\pi gr$$

where T is the absolute temperature, g is the viscosity, K is the Boltzmann constant, and r is the radius of droplet.

9.9. Scattering techniques:

Scattering methods are commonly used to study the dynamics and structure of microemulsions. Techniques such as Small-Angle X-ray Scattering (SAXS), Dynamic Light Scattering (DLS), Photon Correlation Spectroscopy (PCS), and Small-Angle Neutron Scattering (SANS) are among those applied. SAXS provides structural information on macromolecules ranging from 5 to 25 nm in size and identifies repeating distances up to 150 nm in partially ordered systems. It is particularly useful for analyzing nanoscale and microscale particle systems, including particle size, distribution, morphology, and surface-to-volume ratios. SANS is employed to determine droplet size and shape, where "droplet" refers to micelles, oil-swollen micelles, or mixed micelles. The technique relies on interference effects of wavelets scattered from materials in the sample.
A key limitation of these approaches is the need for sample dilution to minimize interparticle interactions, which can alter the pseudo-ternary phase structures and compositions. However, effective results have been obtained by maintaining droplet identity during dilution procedures. Additionally, incorporating deuterated or protonated molecules in SANS enhances the scattering properties of specific microemulsion pseudo-phases. DLS and PCS measure the variation in scattering frequency caused by Brownian motion of the droplets, providing further insights into their behavior.

9.10. Test of thermodynamic stability:

The physical stability of a formulation is super important for it to work properly. If the chemical in the excipient matrix starts to solidify, it could impact how effective the drug is. When the formulation isn’t stable enough, the different components can separate, which reduces how well the drug is absorbed and lowers its therapeutic benefits. Plus, if the formulation doesn’t interact well with the gelatin capsule shell, it might lead to issues like

brittleness, softness, or the drug being released too slowly or incompletely. That's why specific tests are done to check and ensure everything stays stable and effective.

9.11. Turbidimetric test:

Turbidity is a measurable property that helps estimate droplet size and the time it takes for self-emulsification to happen. To test this, a specific amount of SEDDS is added to a fixed volume of suitable liquid, which is continuously stirred at 50 rpm using a magnetic stirrer, all under ideal temperature conditions. A turbidity meter is then used to measure the cloudiness of the mixture. Since the emulsification process is super quick, it's not possible to measure how fast the turbidity changes. Instead, turbidimetric analysis is used to track how the droplets form and grow after emulsification is complete.

9.12. Determination of self-emulsification time:

The emulsification efficiency of various formulations comprising Tween 85 and medium-chain triglyceride systems was analyzed using a nephelometer and a rotating paddle to make easy for the emulsification process. This approach enabled precise measurement of the emulsification duration. Post-emulsification, particle size was assessed using photon similarity spectroscopy, comparing the characteristics of self-emulsified systems with those of homogenized formulations. The self-emulsification process was further examined using light microscopy, revealing that emulsification occurs through the shedding of a thin cloud of microscopic particles from the surface of larger droplets, rather than through a gradual reduction in droplet size. This detailed analysis highlights the intricate nature of the emulsification mechanism.

10. APPLICATION:

Self-emulsifying drug delivery systems (SEDDS) have a wide range of applications in the pharmaceutical field, particularly for enhancing the delivery of poorly water-soluble drugs. Here are some key applications:

10.1. Improved Bioavailability:

I. SEDDS enhance the solubility and absorption of drugs belonging to Biopharmaceutical Classification System (BCS) Class II and IV, which are poorly water-soluble.
II. They form fine emulsions or microemulsions in the gastrointestinal tract, increasing the surface area for drug absorption.

10.2. Oral Drug Delivery:

I. SEDDS are particularly useful for oral administration, as they bypass the hepatic first-pass metabolism by promoting lymphatic absorption.
II. This leads to improved systemic availability of lipophilic drugs.

10.3. Reduction of Gastric Irritation:

By encapsulating the drug in an emulsion, SEDDS minimize direct contact of the drug with the gastric mucosa, reducing irritation.

10.4. Targeted Drug Delivery:

SEDDS can be tailored for targeted delivery, such as to the lymphatic system, which is beneficial for drugs used in cancer therapy or immune modulation.

10.5. Versatility in Dosage Forms:

SEDDS can be formulated into various dosage forms, including capsules, tablets, and powders, making them adaptable for different therapeutic needs.

10.6. Applications in Nutraceuticals:

SEDDS are also used in delivering bioactive compounds in nutraceuticals, such as vitamins and omega-3 fatty acids, to enhance their bioavailability. These systems represent a promising approach to overcoming challenges associated with poorly soluble drugs.

11. CONCLUSION:

Self-emulsifying drug delivery systems (SEDDS) are innovative formulations designed to enhance the solubility and bioavailability of poorly water-soluble, hydrophobic drugs, significantly improving oral drug delivery. These systems create fine oil droplets or micelle dispersions in gastrointestinal (GI) fluids, boosting drug absorption. However, the formulation efficiency of SEDDS is highly case-specific, requiring careful optimization of their composition. SEDDS often employ high concentrations of surfactants, necessitating a balance between their emulsification efficiency and potential toxicity. Two critical factors influencing GI absorption are the size and charge of the oil droplets formed in the emulsion. Advanced SEDDS

formulations have been developed to address certain limitations of conventional systems, including self-microemulsifying systems, pre-formulated freeze-dried emulsions, surfactant dispersions, microencapsulated emulsions, self-emulsifying pellets, solid self-emulsifying systems, and lipid or cross-linked polymeric matrices. These modifications allow better stability, controlled drug release, and more refined self-emulsification processes.

Several pharmaceutical products, such as cyclosporine A (CsA), ritonavir, and saquinavir, have successfully utilized SEDDS for improved therapeutic efficacy and are currently available on the market. With approximately 40% of new drug candidates being hydrophobic, the importance of SEDDS in the pharmaceutical industry is expected to grow, paving the way for more effective solutions to drug solubility and bioavailability challenges. These systems remain at the forefront of modern drug delivery innovation.

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