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Literature Review

Advancement in Formulation Strategies for Microemulsion and Self Emulsifying System: A Comprehensive Review

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Abstract

The low bioavailability, high intra- and inter-subject variability, and lack of dose proportionality problems of hydrophobic (water-repelling) medications can be improved with the help of the self-micro emulsifying drug delivery system (SMEDDS). For poorly soluble medications, self-emulsifying drug delivery systems (SEDDS) are a useful technique for improving solubility and bioavailability. The components of SEDDS and isotropic mixes are oils, surfactants, and occasionally cosolvents. Since thee formulations and methods can result in microemulsions or fine oil-in-water (o/w) emulsions following mild stirring and water phase dilution in the GI tract, they can be a good choice for lipophilic drugs with dissolution rate-limited absorption. This paper provides an overview of the many biopharmaceutical components, kinds, production processes, attributes, constraints, and potential applications of SEDDS. The development of the solid self-emulsifying dosage form and delivery mechanism for SEDDS is emphasized, as is the assessment of SEDDS and its applications.

Keywords: Bioavailability; Drug Delivery System; Liposomes; Microemulsion; Oil-In-Water; Poor Water Solubility; Self-Micro Emulsifying

Introduction

These days, the problem of inadequate bioavailability is associated with the oral administration of such medications; around 35–40% of novel therapeutic candidates have low water solubility [1]. Many formulation techniques, such as complexation, particle size reduction, lipids, surfactants, cyclodextrins, and micelles, have been employed to overcome these problems. Self-micro emulsifying nanoparticles are regarded as an advanced use in medication delivery systems [2].

To improve the bioavailability of certain medications, a range of strategies are used, including microemulsion, pH adjustment, βcyclodextrin complex, and salt arrangement [5]. SMEDDS is the preferred and most successful method for boosting oral bioavailability. A particular form of emulsion called SMEDDS has drawn interest because it can increase the oral bioavailability of poorly soluble drugs [6].

For the oral administration of highly hydrophobic medications, a relatively novel drug delivery method called the self-emulsifying drug delivery system (SEDDS) or self-micro emulsifying drug de-

livery system (SMEDDS) is used. Using the SMEDDS formulation process, the medication is suspended or dissolved in an oil phase together with a surfactant and a co-surfactant or solubilizer [7,8]. This system creates an almost immediate fine oil-in-water (o/w) emulsion when diluted with an aqueous phase and gently stirred. This is the main idea that powers the system [9]. Therefore, when these formulations are ingested orally, the stomach and intestine's composition and digestive motility supply the aqueous phase and agitation needed for in vivo self-emulsification in the gut lumen [10]. The surfactant and co-surfactant exhibit preferential adsorption at the interface upon introduction into aqueous media, thereby reducing interfacial energy and functioning as a mechanical barrier to coalescence [11].

Benefits of sedds as compare to conventional emulsion

While typical emulsions require intense shear to generate a dispersion, the SEDDS preparation method includes dissolving the medication in oil and mixing it with surfactants and cosurfactants [13]. Emulsion instability is most frequently caused by creaming, coalescence, breaking, and phase inversion, among other things. Conversely, SEDDS formulations exhibit physical stability due to their resistance to minor temperature fluctuations, transparency, and isotropy [14]. Furthermore, patient-friendly hard or soft gelatin capsules can be employed to give the final dosage forms of SEDDS formulations [17]. They maintain dose constancy and are ideal for blister or strip packaging. Because the dispersion media and droplets in conventional formulations are heterogeneous, efficacy may suffer, necessitating the use of large, unmanageable containers [18].

Self micro emulsifying drug delivery system

SMEDDS are isotropic mixtures of synthetic or natural oils, solid or liquid surfactants, or hydrophilic solvents and cosolvents/surfactants combined. These mixtures are remarkably effective in producing fine oil-in-water (o/w) microemulsions that can be gently agitated before being diluted in aqueous media like digestive juices. The agitation required for self-emulsification is provided by the stomach and intestine's digestive motility, which permits SMEDDS to freely travel throughout the GI tract [19,20]. The main difference between self-emulsifying drug delivery systems (SMEDDS) and self-emulsifying oil formulation (SEOF) is that SMEDDS generates transparent micro emulsions with droplet sizes smaller than 100 nm, while SEDDS usually generates opaque emulsions with droplet sizes between 100 nm and 300 nm. Moreover, SMEDDS has 20% less oil than SEDDS, which has 40%–80% more [21]. These methods have the potential to boost absorption rate and extent while producing more consistent blood-time profiles in the case of lipophilic medicinal substances, when absorptionis limited by dissolution rate [23]. An essential first step is to choose a suitable blend of oil surfactants that will dissolve the medication at the necessary therapeutic concentration. It is possible to fill soft and hard gelatin capsules with the SMEDDS combination [24].

Advantages of smedds

- Because of the existence of SMEDDS and an increase in specific surface area that promote more efficient drug transport through the gut, oral bioavailability is increased when a drug is in its GIT-insolubilized and micro-emulsified form. Apart from its role as a carrier, the oil phase can also protect against enzyme attack and degradation by acting as a "shield" [26].
- The manufacture of SMEDDS requires simple, inexpensive equipment, which makes them easy to scale up. Examples of this equipment include a basic mixer with an agitator and volumetric liquid filling equipment.
- A reduction in the variations in dietary effects and absorption between and between persons. Food has no effect on SMEDDS performance [27].
- Ability to transfer peptides that are prone to enzymatic hydrolysis in the GIT.
- The activity of p-glycoprotein can be inhibited by SMEDDS, improving oral absorption [28].

Disadvantages of smedds

- GIT irritation may result from medication chemical instability and excessive surfactant content.
- Before their strength can be assessed, in vitro models must undergo additional development and validation.
- The hydrophilic solvent's dilution impact may cause the medicine to have a strong precipitation tendency upon dilution.
- Validating a formulation with multiple excipients becomes more difficult [30].

Review of Literature

Lipid-based drug delivery vehicles represent one of the most widely used strategies for improving the stability of APIs administered orally. The literature indicates that there is much discussion about the proper nomenclature for lipid-based methods. The initial droplet size is not the main factor that determines micro and nano emulsions (SMEDDS and SNEDDS). Use the term SNEDDS if the droplet size of the emulsion is in the nanoscale range. SEDDS are combinations of oil and surfactant that can be rapidly emulsified in water with a mild stirring (Tran and Park, 2021) [31]. SEDDS's chemical makeup and physical characteristics played a significant role in determining how and when to employ them. According to Ujhelyi., *et al*. (2018), these parameters must therefore be established during th0e preformulation stage [33]. Oral absorption of many proteins and therapeutic peptides is low. Technologies to get beyond the GI tract's absorption membrane and enzymatic limitations have been researched. SEDDS have drawn a lot of interest lately as potential carriers for protein and peptide delivery orally (Leonaviciute and Bernkop-Schnürch, 2015) [34]. Drugs, lipids, and surfactants combined in an isotropic mixture that usually contains one or more hydrophilic cosolvents or coemulsifiers with droplet sizes ranging from a few nanometers to several microns make up self-emulsifying drug delivery systems. Natural or synthetic oils, solid or liquid surfactants, and droplet sizes ranging from 10 nm to 100 nm make up the self-micro emulsifying drug delivery system (Sapra K *et al*. 2012) [35]. Oral delivery is the process of dissolving substances that are not particularly soluble in water in a suitable solvent and then packing the mixture into capsules. This method's primary advantage is that it predissolves the molecule, so avoiding the first rate-limiting phase of particle dissolution in the GI tract's aqueous environment. But when the formulation spreads throughout the digestive system, the medication may precipitate out of solution if a hydrophilic solvent (like polyethylene glycol) is utilized. If the drug can dissolve in a lipid carrier, it will be less likely to precipitate upon dilution in the GI tract because partitioning kinetics favor medication retention in lipid droplets. (Meinzer, Vonderscher, and Mueller, 1995). The mechanism of self-emulsification is unknown. Reiss states that self-emulsification happens when the entropy shift in favor of dispersion is greater than the energy needed to make the dispersion's surface area larger [36].

Niosomes were initially described in 1979 by Handjani-Vila., *et al*. These are nonionic surfactant vesicles, with hydrophilic surfactant heads positioned both outside and inside the bilayer and hydrophobic tails enclosed inside. Similar to liposomes, niosomes may include lipophilic or hydrophilic materials [37]. Additionally, the cholesterol found in niosome structure makes the bilayer more stiff and slows down drug release. In terms of loading capacity, stability both chemically and physically, and cost of manufacturing, niosomes are better as carriers than liposomes [38]. Liposomes are spherical vesicles with an aqueous compartment surrounded by phospholipids, either naturally occurring or synthesized. They may have one or many lamellar layers. They were first introduced by Bangham., *et al*. in 1965. Consequently, it has been found that liposomes are a very efficient biocompatible and biodegradable route of administration for both hydrophilic and hydrophobic medications. Drug delivery methods based on liposomes have the benefit of reducing systemic and target toxicity while enabling accurate targeting and the accomplishment of the intended result. Consequently, numerous liposome formulations have been licensed for commercial use, including Ambisome® (amphotericin B), Depocyt® (cytarabine), DepoDur® (morphine sulfate), and others. However, the reticuloendothelial system's quick clearance of liposomal formulations and their lackluster stability restrict their broad application [39].

Objective

This review paper's main goal is to compile information about the creation and evaluation of SMEDDS. The bioavailability of a weakly water soluble drug can be increased by using this information in a number of oral therapies. In order to act as a reference guide for different research scholars and researchers working on self-microemulsifying drug delivery systems, this review article analyzes and summarizes a wide range of literature. Several search engines, including Google, Yahoo, and Bing, were utilized to locate relevant keywords for this manuscript. This article reviews recent work on SMEDDS and provides an overview. This page summarizes the SMEDDS and contains a study of public domain literature related to its development.

Results and Discussion

Self micro emulsifying drug delivery system (SMEDDS)

With minimal agitation from peristalsis movement, these devices can create fine oil in water (o/w) emulsions or microemulsions (self-micro emulsifying drug delivery systems), which can then be

diluted in aqueous media like GI fluid. The agitation required for self-emulsification is provided by the GI tract's good spreadability of self-micro emulsifying formulations and the stomach's and intestine's digesting motility [40]. While SEDDS frequently creates an emulsion with droplet sizes ranging from 100 nm to 300 nm, SMEDDS produces a transparent microemulsion with droplet sizes smaller than 50 nm. Permeability and dissolution are encouraged by the addition of medications to SMEDDS in a well-proportioned distribution with small droplet sizes. SMEDDS have an additional benefit over simple oily solutions in that the medicine can be split between the oil and water thanks to their large interfacial area [41].

Difference among of emulsion and microemulsion

Lipids	Surfactants	Cosurfactants	Cosolvents
Labrafac CC	Tween 85	Hexanol	Ethanol
Isopropyl myristate	Span 20	Pentanol	PEG
Capmul MCM	Capryol 90	Octanol	Carbitol
Maisine 35-1	Lauroglycol 90	Ethanol	Transcutol P
Akoline MCM	Labrafil M 1944 CS	PEG 400	PG
Capmul MCM C-8	Cremophor EL	Labrasol	Glycerin
Capmul GMS-50K	Cremophor RH40	Transcutol P	Tetrahydrofurfuryl alcohol
Labrafil M 1944 CS	Acconon MC8	Capryol 90	Methoxy PEG
Brij	Tween 20	Capyrol PGMC	Isopropanol
Stepan GDL	Labrasol	PEG 300	Butanol
Caprol ET	Tween 80	PEG 600	Benzyl alcohol
Labrafac 1349	Pluronic F 127	PG-dicaprylate/dicaprate	PEG ether (glycofurol)
Labrafac PG	Pluronic L 64	Carbitol	Ethylene glycol
Labrasol	Tagat TQ	Akoline MCM	PG
Lauroglycol 90	Span 80	Tween 85	Glycerol

SMEDDS: Self-microemulsifying drug delivery system, PEG: Polyethylene glycol, PG: Propylene glycol

Table I: Comparison of Emulsion vs Microemulsion

When a mixture of oils, surfactants, co-surfactants, and soluble medicine components is gently shaken and exposed to an aqueous phase, it spontaneously emulsifies to produce a fine oil in water emulsion. This process is known as self-microemulsifying [42]. When it entered the gastrointestinal tract, it spread quickly due to the motility of the small intestine and stomach. SMEDDS clear translucent micro emulsion and SEDDS emulsion will spontaneously form globules upon aqueous dilution, contingent upon the relative composition, screening, and selection of the oil, surfactant, and co-surfactant [43]. The ideal concentrations of oil, surfactant, and co-surfactant for self-emulsification can be found using a pseudo-ternary phase diagram. Moreover, the microemulsification's drug loading affinity is evaluated. The enormous surface area of SMEDDS globules, which are less than 50 nm, enhances the release and absorption of medication. The pharmaceuticals in liquid SMEDDS are present in an oil phase in a dissolve condition, preventing a delayed and rate-limiting dissolution process for hydrophobic medications [44].

The liquid SMEDS are supplied orally via soft and hard gelatine capsules. SMEDDS is founded on the idea that fine oil-in-water microemulsions can be created with gentle agitation. The self-microemulsifying drug delivery system's weakly soluble medications improved drug absorption through restricting enzymatic degradation, boosting intestinal lymphatic transport, speeding up drug solubility, and inhibiting P-glycoprotein (Pgp) activity [45]. Ordinary emulsions are delicate and metastable dispersed forms

that require significant shear of agitation to develop, which makes them unstable. SMEDDS can be taken orally in soft or hard gelatine capsules, are easy to make, and produce microemulsions with little agitation. Additionally, they are physically stable. However, the incompatibility issue with soft gelatine capsule shells arises during the production of liquid SMEDDS in both hard and soft gelatine capsules. As a result, a solid SMEDDS with a high patient acceptability was introduced [46].

Mechanism for self emulsifying

It is unclear what mechanism self-emulsification is based on. Considering all of this, it has been suggested that self-emulsification happens when an entropy shift produces the energy needed to raise the surface region of the dispersion above equilibrium [47]. In a basic emulsion preparation, the free energy directly reflects the energy needed to establish the most recent interface between the oil and water phases. In order to reduce the interfacial area and hence satisfy the free energy of the system, the two phases of the emulsion eventually separate.. Following figure illustrates how oral SMEDDS treatment affects oral drug delivery [48].

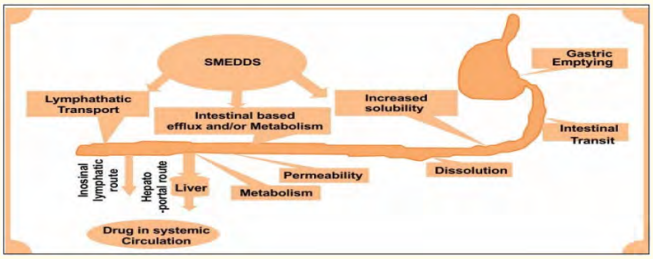

Figure 1: Mechanism for effect about self-micro-emulsifying drug delivery device in oral medication administration [49].

Microemulsion formation

The interfacial tension (γ) between oil and water stays constant during emulsification, while the size of bulk oil (A1) droplets decreases, increasing surface free energy (ΔA γ) and entropy [50]. A microemulsion formed from SMEDDS can be defined by ΔG=γ ΔA-T ΔS, according to the second law of thermodynamics. Here, ΔG stands for formation free energy, ΔS for system change in entropy, γ for interfacial tension, and T for system temperature.

A positive ΔG value indicates that the system creation is non-spontaneous and unstable. In a given system combination, the change in entropy (TΔS) and surface area (ΔA) in the preceding mathematical formula are constant. Zero interfacial tension (γ) creates negative free energy in the system, promoting spontaneous emulsification and thermodynamic stability. The purpose of the SMEDDS formulation should be to reduce interfacial tension. In order to support the surfactant activity in lowering interfacial tension, a co-surfactant can be added as a third component to obtain the ultralow interfacial tension. CMC falls before γ approaches zero when surfactant concentration is raised to lower interfacial tension.

Components of SMEDDS

Lipid

Lipids are essential for the solubility of medications in gastrointestinal (GI) fluids, the fluidization of intestinal cell membranes, the solubilization of hydrophobic pharmaceuticals, and the acceleration of dissolution rates. Furthermore, by modifying the pharmaceutical properties of the drug, lipids shield it from enzymatic and chemical degradation. The majority of medications used in SMEDDS are hydrophobic, meaning they dissolve better in triglycerides than surfactants do. They are therefore utilized at a 40% – 80% concentration. Table I provides an overview of the different lipids employed in SMEDDS.

Surfactant

Surfactants are used at concentrations ranging from 30% to 60%. They play a significant role in increasing the solubility of hydrophobic drugs in oil, dispersing liquid vehicles in GI fluids upon dilution, enhancing permeability to improve bioavailability, preventing precipitate formation within the GI lumen, and prolonging the drug's solubility, which leads to effective absorption. By accumulating at the oil-water interface and settling in the inner stage (internal phase) of the emulsion, they create a microemulsion that is more stable. The various surfactants employed in SMEDDS are presented in Table I.

Cosurfactant

In order to reduce interfacial tension, SMEDDS calls for high dosages of surfactants, which might irritate the stomach. As a

result, cosurfactants are used to reduce the concentration of surfactant, dissolve a significant amount of hydrophilic or lipophilic medication in lipid base, and lessen the oil/water interface, all of which lead to the instantaneous micro-emulsion. When used with surfactants, cosurfactants with hydrophile-lipophile balance (HLB) values between 10 and 14 are frequently used to significantly lower interfacial tension, provide a short negative value, and provide sufficient flexibility to the interfacial layer. The many cosurfactants utilized in SMEDDS are listed in Table I.

Cosolvents

Propylene glycol, polyethylene glycol (PEG), and ethanol are examples of cosolvents used in oral dosage forms. They enhance the solubility of the drug or surfactant in a lipidic base and aid in the dispersion process by starting the early stages of dispersion. They are also useful in microemulsion systems as co-surfactants. Alcohol and other volatile solvents migrate into the soft gelatin capsule shell, causing lipophilic medications to precipitate. The disintegration ability of lipophilic drugs made of alcohol-free materials is restricted. Therefore, the proper solvent is selected at the same time as the components. The cosolvents that are frequently utilized in SMEDDS are displayed in Table I.

Lipidic formulation system

Based on the excipients employed, lipidic formulations are categorized as Type I, II, III, or IV. While Type I formulations do not self-emulsify, Type II, III, and IV formulations do. The type of emulsion that forms when water is added to the self-emulsifying system is determined by the excipients that were utilized in the formulation. These elements also affect how easily lipid compositions can be digested. Components of the lipidic system are covered in the next section. The classification scheme for lipid formulation is displayed in Table II.

Formulation	Excipients	Properties	Pros	Cons
Type I	Oils lacking of surfactants (e.g. tri-,di-and mono glycerides)	Not dispersing, it needs digestion.	Simple, Compatibility is excellent for capsule.	Formulation has poor solvent capacity unless drug is highly lipophilic.
Type II	Oils and water-insoluble surfactants.	SES formed without water-soluble components	Unlikely to lose solvent capacity on dispersion	Turbid o/w dispersion (particlesize0.25–2 mm)
Type III	Oils, surfactants and co solvents (both water insoluble and water-soluble excipients)	SES/SMES formed with water-soluble components	clear or almost clear dispersion; drug absorption without digestion	Possible loss of solvent capacity on dispersion; less easily digested
Type IV	Water-soluble surfactants and Co solvents(no oils)	Formulation disperses typically to forma micellar solution	Formulation has good solvent capacity for many drugs	Likely loss of solvent capacity On dispersion; might not be digestible

Table II: The Lipid Formulation Classification System lists the attributes, advantages, and disadvantages of the four main "lipid" formulation types.

Summary

Self-Micro emulsifying Drug Delivery Systems (SMEDDS) are a promising approach to enhance the bioavailability of poorly water-soluble drugs. These lipid-based systems increase drug solubility and permeability, leading to better absorption and reduced first-pass metabolism. SMEDDS are relatively easy to manufacture and can be customized with various oils, surfactants, and co-surfactants to optimize drug delivery. However, careful selection of these components is essential for successful formulation and achieving desired therapeutic outcomes.

Conclusion

SMEDDS offer a valuable strategy for improving the delivery of poorly water-soluble drugs. By optimizing their formulation, researchers can enhance drug bioavailability, reduce dosage requirements, and improve patient outcomes.

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