A BRIEF REVIEW ON SELF MICRO EMULSIFYING DRUG DELIVERY SYSTEM

Sweta Bhardwaj, N.S.Ganesh, Gopinath E, Vineeth Chandy

ABSTRACT

The pharmaceutical industry faces a significant challenge with orally administered drugs' low aqueous solubility, which causes poor dissolution and low solubility and results in high intra- and inter-subject variability and a lack of dose proportionality for nearly 35–40% of newly launched drugs. Numerous techniques, including salt creation, solid dispersion, and complex formation, might augment this. The Self Emulsifying Drug Delivery System (SEDDS) is becoming more and more well known for enhancing the solubility of lipophilic medicines. SEDDS are described as isotropic combinations of one or more hydrophilic solvents and cosolvents/surfactants that have the unusual ability to create fine oil-in-water (o/w) micro emulsions with modest agitation followed by dilution in aqueous media, such as GI fluids. SMEDDS are designed to increase the oral solubility of lipophilic medications. It is an isotropic mixture of substances including oil, surfactant, co-surfactant, and medication with the unusual ability to agitate and dilute to create fine o/w micro-emulsion. Its liquid formulation method improved poorly water soluble medications' absorption and solubility, but it also had several disadvantages, such as long-term stability concerns and storage conditions. To get around these issues, specific techniques turn liquid dosage forms into solid dosage forms. The current research provides in-depth knowledge on formulation design using excipient screening. We research the choice and solubility of excipients, their manufacture and characterization, and the mechanism by which solubility might be increased. This discussion will help you comprehend SMEDDS's most recent developments, commercial formulation, and SMEDDS-related patents. Poorly water-soluble medications with low absorption and dissolution rates can be efficiently formulated as SMEDDS to produce a stable plasma profile. The poorly water soluble medication's plasma levels demonstrate the crucial stage of drug absorption known as dissolution.

Keywords:*Self emulsifying drug delivery system(SEDDS),Solid self emulsifying drug delivery system(S-SEDDS),Surfactants,Oils*

INTRODUCTION

Self-emulsifying systems were developed in the 1960s, combining lipidic and hydrophilic chemicals with water-insoluble insecticides and other lipophilic excipients to improve their efficacy. Pouton originally disclosed the development of SEDDS, a method for overcoming the numerous challenges faced by lipophilic medicines, in 1985. Since the 1960s, extensive research has been done to improve the bioavailability of medications and the transition of technologies from the research laboratory to the industrial scale and then to the clinics[1].

In many disorders, oral administration is the most common route of delivery. Reduced bioavailability, which specifically results from water solubility, is a major issue with oral medication administration[2].

Approximately 40% of current medication applications have limited water solubility, which presents a challenge for the development of the most effective oral solid dosage form[3]. Solubility is one of the most crucial factors to consider when choosing a medicine to be preferential attention in the systemic stream for a better therapeutic response. Problems with dose uniformity are caused by a drug's poor solubility in the circulatory flow. Most of the active ingredients are found to be weakly water soluble[4].

Several methods were employed to address these issues, including altering the solubility or keeping the drug dissolved during gastrointestinal transit. Drugs that are poorly water soluble are made more orally bioavailable using a variety of methods[6]. Due to its high level of patient compliance, the oral route has been the primary medication delivery method for the long-term management of numerous disorders. The high lipophilicity of the medicine itself, however, makes it difficult for 50% of the drug molecules to be delivered orally.6 In terms of formulation design and bioavailability of new pharmaceutical products, about 40% of novel drug candidates have low solubility in water, which presents a difficulty in the development of the ideal oral solid dosage form[7].

There are numerous methods for overcoming these issues, including changing the solubility or keeping the medicine dissolved during the stomach transit time. These techniques may involve the use of surfactants, cyclodextrins, micronization, liquidsolid techniques, salt creation, pH change, nano size delivery, solid dispersions, and permeation enhancers[8].

Lipid solutions, emulsions, and emulsion preconcentrates have received a lot of attention since they can be created as physically stable formulations suited for encapsulating such poorly soluble medicines[9]. Emulsion systems come with their own set of difficulties, such as manufacturing issues and stability issues related to their industrial output. Self-emulsification systems are one formulation method that may provide a suitable solution to such issues[10].

The term "self-micro emulsifying drug delivery system" (SMEDDS) refers to isotropic mixtures of natural or synthetic oils, solid or liquid surfactants, or alternatively, one or more hydrophilic solvents and co-solvents/surfactants that have the unusual ability to form fine oil-in-water (o/w) micro emulsions upon mild agitation followed by dilution in aqueous media, such as GI fluids[11].SMEDDS disseminate easily in the GI tract, and the stomach's and intestine's digesting motion causes the agitation required for self-emulsification. Self-emulsifying drug delivery systems (SEDDS), also known as self-emulsifying oil formulation (SEOF), and SMEDDS are fundamentally different from one another[12]. SEDDS typically produce opaque emulsions with droplet sizes between 100 and 300 nm, while SMEDDS form transparent micro emulsions with droplet sizes of less than 50 nm. SMEDDS are physically stable formulations that are simple to make when compared to emulsions, which are delicate and metastable dispersion forms. Also, there are a number of distinctions between SMEDDS and standard emu?lsions[13]./

PURPOSE

- Effective drug incorporation is a crucial factor to take into account when creating solid SES, both in terms of the drug's solubilization within the oil surfactant mixture to enable the formation of a suitable solid dosage and the potential impact the drug may have on the emulsification properties once formed.
- If an increase in oral bioavailability is proven, the benefit of solid SES lies in its dose reduction[14].

NEED OF SMEDDS

Poorly water-soluble substances can be taken orally by first pre-dissolving them in a suitable solvent and then putting the formulation into capsules. The fundamental advantage of this strategy is that by pre-dissolving the chemical, the rate-limiting phase of particle dissolution in the GIT's aqueous environment is avoided. As partitioning kinetics will favour the drug staying in the lipid droplets, the risk of precipitation on dilution in the GIT is reduced if the medication can be dissolved in a lipid vehicle[15].

Another method for improving the solubility of medications that are poorly soluble is to synthesize them in a solid solution using a water-soluble polymer. This type of formulation could have one drawback in that the medication may favour a more thermodynamically stable state, which could lead to the compound crystalizing in the polymer matrix[16].

ADVANTAGES

1. The SMEDDS formulation helps ensure that the medicine is distributed widely along the GIT and is promptly delivered through GIT, reducing the irritation that can result from prolonged contact between the drug and the stomach wall[17].

2. These formulations produce fine droplets with a broad interface when dispersed in water because the active ingredient can easily be transported from the oil phase to the aqueous phase, which is not to be expected with oily solutions carrying lipophilic active ingredient.
3. SMEDDS have an advantage over emulsions in terms of stability thanks to their low energy consumption and straightforward manufacturing method. The formulation of SMEDDS only requires basic mixing tools, and it takes less time to prepare than emulsions[18].
4. The poor water-soluble pharmaceuticals with dissolution rate absorption limitations can be efficiently synthesized in the form of SMEDDS, resulting in a stable plasma profile. The poorly water-soluble medication's steady plasma levels demonstrate the crucial stage of drug absorption known as dissolution.
5. The formulation of SMEDDS helps prevent medications that are prone to chemical and enzymatic degradation in the GIT since the medication is administered to the body as oil droplets[19].
6. Pre-concentrated microemulsions have an advantage over those that are administered as liquid-filled soft gelatin capsules.
7. SMEDDS are preferable to SEDDS because the latter are less dependent on bile salts for droplet formation, which is believed to result in greater active ingredient absorption in comparison to SEDDS.
8. Due to their loosening impact on tight junctions, surfactants with a high HLB value, such as Tween 80, are reported to improve the permeability of active substances when provided together with the formulation[20].
9. In addition to lipids, typical surfactants included in SMEDDS formulations such Tween 80, Spans, Cremophors (EL and RH40), and Pluronic's are claimed to have an inhibitory impact on efflux transporters that aid in enhancing the bioavailability of the medications. Tocopheryl polyethylene glycol succinate 1000 (TPGS), a surfactant made by esterifying polyethylene glycol 1000 with vitamin E succinate, inhibits the activity of efflux transporters such Pglycoprotein. A formulation incorporating the surfactant polysorbate 80 inhibits the release of paclitaxel from the GIT[21].
10. Novel ways to deal with improve water solvency and extreme bioavailability of lipophilic medications[22].

APPLICATIONS

- **ADVANCED OIL RECOVERY USING MICROEMULSIONS**

  It has been attempted to investigate the mechanics of improved oil recovery (EOR) employing surfactant and microemulsion flooding. The EOR procedure can extract about 20% of the remaining underground oil that cannot be recovered. Because to the strong interfacial tension (about 20–25 mN/M) between the crude oil and reservoir brine, the oil is still trapped in the reservoir. A significant portion of the trapped residual oil in the porous media can be mobilized if the interfacial tension can be lowered to around 10-3 mN/m. The system's low interfacial viscosity is also beneficial.

- **FUEL FROM MICROEMULSIONS**

  The inclusion of water in a stable microemulsion, which is one of the direct benefits of microemulsion-based fuels, is successfully exploited to prevent soot production. Lower heat release and combustion temperature result from the water vaporization that occurs during combustion. Carbon monoxide and nitrogen oxide emission rates will drop as a direct result[23].

- **MICROEMULSIONS IN TEXTILE FINISHING AND COATINGS**

  Because the micro emulsified resins address many of the drawbacks of the more established water-based systems without posing the same health and environmental risks as solvent-based coatings, the coating application area is a very promising and quickly expanding field of microemulsion technology. Microemulsions are perfect when stability and uniformity of the final product are sought because of their stability and small droplet size.

- **LUBRICANTS, CUTTING OILS, AND CORROSION INHIBITORS FROM MICROEMULSIONS**

  Reverse micellar solutions, also known as microemulsions, have been used for many years as cutting fluids, lubricants, and corrosion inhibitors. The microemulsion's surfactant content inhibits corrosion, while the added water content above pure oil results in a larger heat capacity. In addition to being shielded by an adsorbed hydrophobic surfactant coating, the metal surface is prevented from being corroded by corrosive

chemicals due to their solubilization in the microemulsion. Solubilization is selective, though, and in some circumstances, other mechanisms might contribute to the prevention of corrosion.

- **MICROEMULSIONS AS DETERGENCY**
  Microemulsions are promising systems for detergency applications over commonly utilized organic solvents since they can solubilize polar compounds because to their distinctive characteristics (e.g., grease, oil).
  They can spontaneously develop when the components are combined and have low interfacial tension between the aqueous and oil phases[24].

- **FOOD MICROEMULSIONS**
  Natural emulsions are a part of some foods. As a functional condition of lipids, microemulsions have thus been exploited in food preparation. As fat is broken down and absorbed in the intestine, microemulsions are created. Yet, a neglected area of food technology is the possibility of creating microemulsion on purpose and utilizing them as tools in food production.

- **MICROEMULSIONS IN PHARMACEUTICALS**
  In pharmaceutical preparations, liquid crystalline, microencapsulation, and emulsion forming systems are frequently utilized. Negative effects include low micelle solubilization capability and unstable emulsions. Microemulsions are a superior option than other compartmentalized systems due to their simple formation, exceptional environment-independent stability[25].

SELECTION OF EXCIPIENTS

- **OILS**
  Oil is a significant component of SMEDDS because the kind and concentration of oil used in formulation alter solubilization and access to a lymphatic circulation of poorly water-soluble medications. Depending on the method of administration, the choice of oil regulation criteria should be taken into consideration. Lipids are naturally occurring oils and fats made up of triglycerides and fatty acids with varying degrees of unsaturation in their chain lengths. With SMEDDS, the oil selection is crucial since it affects how much of the medicine dissolves in the body[26].

  Various Types of Oils used are:
  - Fixed Oils (Long-chain Triglycerides): Soybean oil, arachis oil, cottonseed oil, maize (corn)oil, hydrolyzed corn oil, olive oil, sesame oil, sunflower oil, palm oil, peanut oil, triolein etc.
  - Medium-chain Triglycerides and Related Esters: Caprylic/capric triglycerides (Akomed E, Akomed R, Miglyol 810 and Captex 355, Crodamol GTCC), fractionated coconut oil (Miglyol 812), Captex 300, Labrafac CC, Triacetin.
  - Medium-chain Mono and Di-glycerides: Mono and diglycerides of capric/caprylic acid. (Capmul MCM and Imwitor).
  - Long-chain Mono Glycerides: Glycerylmonooleate (Peceol, Capmul GMO), glyceryl mono linoleate (Maisine -35)[27].
  - Propylene Glycol (PG) Fatty Acid Esters: PG Diester of caprylic/capric acid (Labrafac PG), PG monocaprylic ester (Sefsol-218), PG monolaurate (Lauroglycol FCC, Lauroglycol 90, Capmul PG-12) PG dicaprylate (Miglyol 840).
  - Caprylic / Capric/diglyceryl Succinate: Miglyol 829.
  - Fatty Acids: Caprylic acid, oleic acid (crossential 094).
  - Fatty Acid Esters: Ethyl butyrate, Isopropyl myristate, Isopropyl palmitate, ethyl oleate (crodamol EO).
  - Vitamins: Vitamin E Mineral oil: Liquid paraffin[28].

- **SURFACTANT**

Surfactants play a significant role in improving the solubility of hydrophobic drugs in oil, dispersing liquid carriers on dilution in GIT fluids, improving bioavailability by increasing permeability, preventing precipitate formation in the GI lumen, and prolonging the presence of drug moiety in soluble form, which leads to effective absorption. 30–60% concentrations of surfactants are typically used. They settle at the inner stage of the emulsion (internal phase) and concentrate at the oil-water contact, creating a more stable microemulsion[29].

Based on the type of hydrophilic group present inside the molecule, surfactant molecules can be categorized.
As outlined below, there are four major categories of surfactants

i. Anionic surfactants

ii. Cationic surfactants

iii. Ampholytic surfactants

iv. Nonionic surfactants

i. **Anionic Surfactants**: These are surfactants that have a hydrophilic group with a negative charge, such as a carboxyl (RCOO-), sulphonate (RSO3-), or sulphate group (ROSO3-).
Examples: Sodium lauryl sulphate, potassium laurate

ii. **Cationic surfactants**: They have a positive charge on the hydrophilic group.
Example: Quaternary ammonium halide

iii. **Ampholytic surfactants**, commonly referred to as zwitterionic surfactants, have both a positive and a negative charge.
Example: Sulfobetaines

iv. **Nonionic surfactants** have a hydrophilic group that is not charged but gets its water solubility from highly polar groups like polyoxyethylene or hydroxyl (OCH2CH2O).
Examples: Sorbitan esters (Spans), polysorbates (Tweens)

SMEDDS are made using nonionic surfactants with high hydrophilic lipophilic balance (HLB) values. To create a stable SMEDDS, the typical surfactant strength ranges between 30 and 60% w/w of the formulation. High HLB and hydrophilicity surfactants help the formulation spread quickly through aqueous medium and/or form o/w droplets right away. Surfactants have an amphiphilic character and have a high solubility or dissolution rate for hydrophobic medicinal molecules[30].

- **CO-SURFACTANTS**

The development of an optimal SMEDDS necessitates somewhat high fixations (often above 30% w/w) of surfactants, yet this leads to Gastrointestinal irritation. In order to reduce surfactant convergence, co surfactant is used[31]. The co-and surfactant's combined job is to reduce interfacial strain to a negligibly small or momentary value. At this point, the interface would widen to form small, dispersed beads and subsequently absorb more surfactants and surfactant/cosurfactants until their mass condition is sufficiently depleted to restore a positive interfacial strain.

The micro emulsions are framed by the "unconstrained emulsification process. Natural solvents that are suitable for oral administration, such as ethanol, propylene glycol, polyethylene glycol (PEG), etc., may help dissolve a significant amount of the hydrophilic surfactant or the medication in the lipid base and act as co-surfactants in one's own emulsifying drug conveyance systems[32].

- **SOLID CARRIERS**

Solid carriers can be microporous inorganic substances, high surface-area colloidal inorganic adsorbent substances, cross-linked polymers, or nanoparticle adsorbents, for example, silica, silicates, magnesium trisilicate, magnesium aluminum silicate (Neusilin) microporous calcium silicate (Florite TM RE) magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose, and cross-linked polymethyl methacrylate can be adsorbed at high levels (up to 70%w/w) onto suitable carriers.

CONCLUSION

A hydrophobic medication's solubility can be increased and improved with the use of the promising drug delivery method known as SMEEDS. While lipid-based formulations are still not very common in commercial formulations, this review article will undoubtedly draw the attention of the new researchers to grasp the role of specific lipids and surfactants utilized for the formulation of SMEDDS.

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