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A REVIEW ON SELF EMULSIFYING DRUG DELIVERYSYSTEM

Miss. Apeksha V. Masal[*1], Mr. Nilesh A. Nalawade[2], Miss. Sharayu S. Ranaware[3], Miss Akanksha B. Yadav[4], Miss. Sukanya P. Paricharak[5], Miss Pallavi G. Dhaware[6], Miss. Swati B. Kavade[7]

Agriculture Development Trust's Shardabai Pawar Institute of Pharmaceutical Science And Research, Shardanagar, Baramati-413115,Maharashtra, India.

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***Corresponding Author**
Apeksha V. Masal
Agriculture Development Trust's Shardabai Pawar Institute of Pharmaceutical Science And Research, Shardanagar, Baramati-413115, Maharashtra, India.

ABSTRACT

Solubility of orally administered drug is a major challenge of pharmaceutical industry as nearly 35 to 40% of newly launched drug passes low aqueous solubility which leads to there are having poor dissolution and low bioavailability. This can be increased by different methods like salt formation, solid dispersion and complex formation. Self Emulsifying Drug Delivery System (SEDDS) is gaining popularity for improving the solubility of lipophilic drugs. SEDDS are defined as isotropic mixtures of one or more hydrophilic solvent/ and co- solvent surfactants that have a unique ability of forming fine oil -in- water (o/w) micro emulsion upon mild agitation followed by dilution in aqueous media, such as GI fluids. Present review article provides a compressive knowledge and updated account of advancements in SEDDS with regard to its composition of excipients, various methods of solidification of liquid SEDDS, and also various Pharmaceutical advantages.

KEYWORDS: Micro emulsion, Drug.

INTRODUCTION TO SELF EMULSIFYING DRUG DELIVERY SYSTEM

In recent years the oral route is the most performed of drug delivery for the treatment of many number of diseases, up to 40% of chemical entity discovered by the pharmaceutical industry. They leads to poor oral bioavailability. Number of effective lipophilic drugs solo oral bioavailability due to their poor aqueous solubility properties. For this class of compounds, gives the" low solubility/ high permeability" class II dissolve in Environmental lumen. Now the day it is a grand challenge for pharmaceutical scientist to transfer molecules

into molecules with good oral bioavailability, to overcome these problem by using the permeation enhancers, micronization, surfactant liquids, salt formation, nanoparticles solid dispersion. Other than all of Treasures one of the most popular and commercial valuable formulation methodologies for solving this problem by self emulsifying Drug Delivery System self emulsion Drug Delivery System have been shown to partially successful in improving in oral bioavailability of water soluble drug. Self emulsifying drug delivery system (SEDDS) are isotropic mixture of oil surfactant solvent and co-solvent/ surfactant. These system its spontaneously to produce Fine oil-in-water emulsion when announced into aqueous phase under gentle agitation.[1-5]

Fig. No. 1: Self-Emulsion and Self-Micro Emulsion.

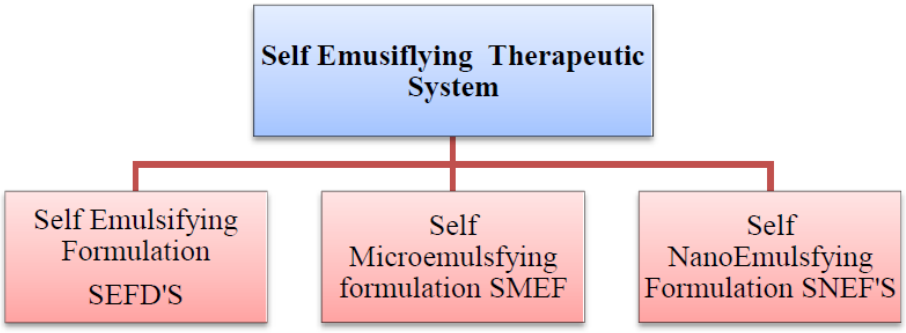

Figure 2: Different Self Emulsifying Lipid Formulation.

Table 1: Features of different Self-Emulsifying Formulations.[6]

SEF's	SMEF's	SNEF's
Oil droplet size 200nm-5µm	Oil droplet size 100-250nm	Droplet size >100nm
Appearance is turbid	Appearance clear totranslucent	Optically clear
Use surfactants of HLB<12	Use surfactants of HLB>12	Use surfactants ofHLB >12
Concentration of oil is 40-80%	Concentration of oil is lessthan 20%	Concentration of oil is lessthan 20%

Approach of Self Emulsifying Drug Delivery System

SEDDS are promising approach fororal delivery of poorly water soluble compound. It can be achieved by pre -dissolving the compound in a proper solvent and then filled into capsules. The oral delivery of hydrophobic drug can be done by SEDDS. The main benefit of this system is that pre-dissolving the drug compound and to overcome the initial rate limiting step of particular dissolution in the aqueous medium within the GI track. If the drug can be dissolved into a lipid vehicles then there is less potential for drug prescription on dilution in GI tract.[5]

Mechanism of self-emulsification

According to 'Reiss' self emulsification arises when entropy changes that favor's dispersion is grater than energy required to increase the surface area of dispersion. The conventional emulsion is direct function of the energy required to create new surface between oil and water phase.

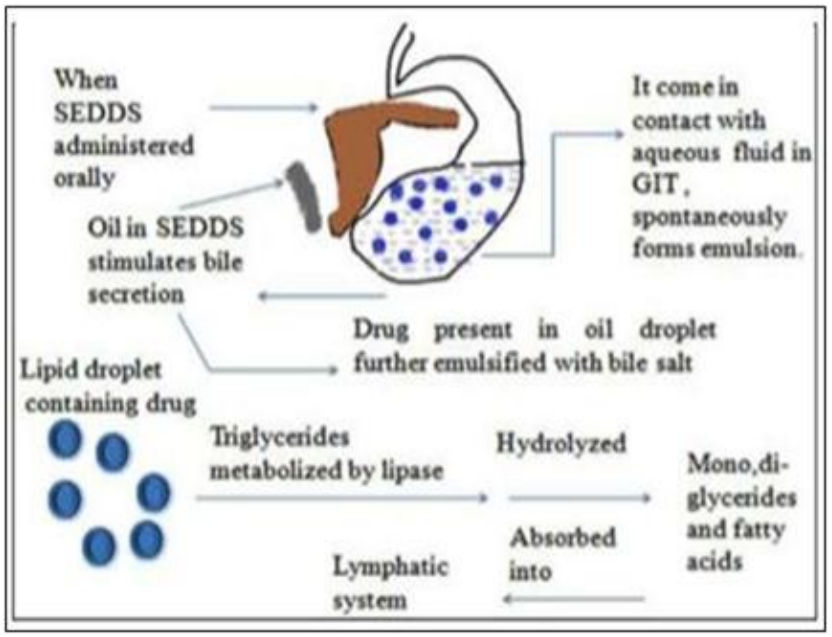

Figure: 3 Mechanism of SEDDS.

It is represented by following Equation

$\Delta G = \sum Niyri$

In which 'N' is the number of droplet with radius 'r' and 'σ', is the interfacial energy. The two phase of emulsion tends to distinct with time to reduced the interfacial area and subsequently, the emulsion is stabilized by emulsifying agent, which forms monolayer of emulsion droplets, and hence reduced the interfacial energy, as well energy a barrier to avoid

coalescence.[7-12]

Excipients used in self emulsifying Drug Delivery System

- **Lipids**

Lipid is a vital ingredient of the SEDDS formulation. It can not only solubilize large amount of lipophilic drugs or facilitate self-emulsification not also improve the part of lipophilic drug transported via intestinal lymphatic system, there by increasing its absorption from GIT. Natural edible oils, comprising medium chain triglycerides, are not frequently preferred in this regard owing to their poor ability to dissolve large amount of lipophilic drugs. Modified long and medium-chain triglycerides oils, with varying degrees of saturation or hydrolysis, have been used widely for the design of SEDDS. These semisynthetic derivatives form good emulsification system used with a large number of solubility enhancing surfactants approved for oral administration.

- **Surfactants:** A surfactant is necessary to provide the essential emulsifying characteristic to SEDDS. Surfactant, being ampiphilic in natures, in variably dissolve high amount of hydrophobic drug. The two issues that govern the selection of surfactant encompass its hydrophilic- lipophilic balance (HLB) and safety. The HLB of surfactant provides vital information ON its possible effectiveness in formulation of SEDDS.

The four main group of surfactants with examples

1. Anionic surfactant: Potassium lauryl, Sodium lauryl sulpahte.
2. Cationic surfactant: Quaternary ammonium halide
3. Ampholytic surfactant: Sulbetaines
4. Nonionic surfactant: Example: Sorbitan ester (Span), Poly-sorbates (Tweens).

- **Co-solvents:** Usually, the formulation of an effective SEDDS requires high concentration of surfactant. Accordingly, co- solvent such as ethanol, propylene glycol and polyethylene glycol are required to enable the dissolution of large amount of hydrophilic surfactant of hydrophobic drug into lipid phase. The lipid mixture with higher surfactant and co-surfactant: oil ration leads to formation of SEDDS. The role of co-solvent together surfactant is too lower the interfacial tension to a very small even transient negative value.Alcohol and other volatile have the drawback of evaporating into the shell of soft or hard gelatin capsules leading to precipitation of drug.[10,13,14]

Development of SEDDS: Preliminary studies are performed for selection of oil, which is an

important and required for formulation of SEDDS. SEDDS contain oil, a surfactant and a co-surfactant. Solubility of drug is determined in various oil and surfactant. Prepare a series of SEDDS system containing a drug in various oil and surfactant. Then, in vitro self-emulsification properties and droplet size study of this formulation upon their addition to water under mild agitation condition is studied. Pseudo- ternary phase diagram is constructed, identify the efficient self- emulsification region. Form these studies, an optimized formulation is selected and its bio- availability is compared with a reference formulation. The efficiency of oral absorption of the drug compound from the SEDDS depends on the many formulation – related parameters, such as surfactant concentration, oil/surfactant ration, polarity of the emulsion, droplet size and charge, all of which in essence determine the self emulsification ability. Thus only very specific pharmaceutical excipient combination will lead to efficient self emulsifying systems.

Construction of phase-diagram: Pseudo ternary phase diagram of oil, surfactant/ co-surfactant (Smix), and water were constructed using the water titration method each of them represents a side of triangle. Ternary mixture with varying composition of surfactant, co-surfactant and oil were prepared. Surfactant and co-surfactant were mixed in different ratio. For each phase of diagram, oil and specific surfactant to co- surfactant ratio were mixed thoroughly in different ratio from 1:9 to 9:1 in different conical flask. Nine different combinations oil and Smix, 1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1, were prepared so that maximum ratio were cover for the study to the boundaries of phase precisely formed in the phase diagrams. A transparent and homogeneous mixture of oil/Smix was formed by stirring for five min and then each mixture was titrated with water and observed for phase clarity and flow ability. The point at which system become bluish or turbid, titration was discontinued and at this point quantity of oil, surfactant and co- surfactant was calculated. These results were then used to determine the boundaries of the self- emulsion domain. Ternary phase diagram were then constructed by using Triangular software.[14,15,6,17]

Solidification Technical Of Self Emulsifying Drug Delivery System

A. Capsule filling with liquid and semisolid SEDDS formulation: Capsule filling is the simplest and most common technology for encapsulation of liquid or

1. Heating of semisolid excipients at least 20 degree C above its meltingpoint.
2. Incorporation of active substance with stirring.
3. Capsule filling with molten mixture and cooling to room temperature.

For liquid formulations, it involves a two-step process : feeling of formulation into capsule followed by sealing of body and cap of the capsule, either by banding or by micro spray sealing Advantages of this technique are simplicity of manufacturing, suitable for low dose highly drug loading potential up to 50% W/W.

B. **Adsorption to solid carriers**: Free flowing powder may be obtained from liquid SEDDS by adsorption to solid carriers. The adsorption process is simple and just involve addition of liquid formulation into carriers by mixing in a blender. The resulting powder may then be filled directly into capsules or alternatively mixed with suitable excipients before compression into tablets. The significant benefit of the adsorption technique is good content uniformity. SEDDS can be adsorbed at high level up to 70% W/W onto suitable carriers. Solid carriers can be micro Porous inorganic substance, high surface are colloidal inorganic adsorbents Substances, cross-linked polymer or for nanoparticle adsorbent example silica, silicates, magnesium trisilicate, magnesium hydroxide, talcum, crospovidone, cross-linked sodium carboxymethyl cellulose and cross linked polymethyl methacrylate. Cross linked Polymers create a favorable environment to sustain drug dissolution and also assist in slowing down drug reprecipitation. Nanoparticles adsorbent compress porous Silicon dioxide, carbon nanotubes, carbon nano horns fullerene, and charcoal and bamboo charcoal.

C. **Spray drying:** In this technique first the prepared SEDDS formulation containing oil, surfactant, drug, solid Carriers etc., is spread into a drying chamber through a nozzle. The volatile vehicle firstly evaporate leaving behind small solid particles. These particles are then filled into capsule or compressed into tablets. According to the drying characteristic of the product and powder specification the atomizer, the temperature, the most suitable air flow pattern and the drying chamber design are selected.

D. **Supercritical fluid based method:** Lipids may be used in supercritical fluid based method either for coating of drug particle or for producing solid dispersions. The solubility of the coating material is sustained initially by elevated pressure and temperature conditions. The coating process is subsequently facilitated by a grand reduction in pressure and temperature leading to reduce solubility of the coating material in the supercritical fluid allowing granule disposition onto the drug particles, to form coating layers. The supercritical fluid of choice is supercritical carbon dioxide. The process for obtaining solid particles dissolving drug and liquid based excipients. In an

organic solvent such as methanol and then in supercritical fluid followed by lowering the temperature and pressure condition to reduce their solubility in fluid. The important consideration with this formulation technique.

1. The solubility of the formulation components in the supercritical fluids.
2. The integrity or stability of the active substance under the processes conditions.
3. The energy or environmental concerns relating to the operation of solvents.

E. Melt granulation: Melt granulation is a process in which powder agglomeration is obtained through the addition of a Binder that meals for softness at relatively low temperatures. As a one step operation melt granulation, offers several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. More over it is also good alternative to the use of solvent. The main parameters that controls the granulation process are impeller I speed mixing time, Binder particle size, and the viscosity of binder. A wide range of solid and semi solid lipids can be applied as meltable binders.

F. Melt extrusion /extrusion spheronization: Melt extrusion is a solvent free process that allows high drug loading up to 60% as well as content uniformity. Extrusion is a procedure in which a raw material with plastic properties is converted into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow, and pressure condition. The size of the extrusion aperture determines the approximate size of the resulting spheroids. The extrusion-spheronization process is commonly used in the Pharma industry to make uniformly sized self-Nano emulsifying drug delivery systems SNEDDS and then tablet can be prepared by extrusion speronization using MCC, malt dextrin crospovidone. The bioavailability of propranolol improved by preparing a matrix-in-cylinder system for sustained drug delivery, consisting of a hot melt extruded ethyl cellulose pipe surrounding a drug containing HPMC-Gelucire44/14 core. This approach has been successfully applied to 17β-estradiol and two model drugs methyl and propyl parabens with surfactants like sucrose monopalmitate, laurel polyoxylglycerides and Polysorbate 80. Applying extrusion- spheronization, SE pellets of diazepam and bi-layered cohesive SE pellets have been prepared.[17,18,19,20]

Advantages of Self Emulsifying Drug Delivery System

- Improvement of oral bioavailability: Dissolution rate dependent absorption is a major factor that limits the bioavailability of numerous poorly water soluble drugs. The ability

of SMEDDS to prevent the drug to GIT in solubilized and micro emulsified form subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability.

- Ease of manufacture and scale-up: Ease of manufacture and scale-up is one of the most important advantages that make SMEDDS unique when compared to other drug delivery system like solid dispersions, liposomes, Nano particles, etc., dealing with improvement of bioavailability. SMEDDS require very simple and economical manufacturing facilities like simple mixer with agitator and volumetric liquid filling equipment for large scale manufacturing. This explains the interest of industry in the SMEDDS.
- Reduction in inter-subject and intra-subject variability and food effects: These are several drugs which show large inter-subject and intra-subject variation in absorption leading to decreased performance of drug and patient non-compliance. Food is major factor affecting the therapeutic performance of the drug in the body.
- Ability to deliver peptide that are prone to enzymatic hydrolysis in GIT: One distinctive property that makes SMEDDS superior as compared to the other drug delivery system is their ability to deliver macromolecules like peptide, hormones, enzyme substrate and inhibitors and their ability to offer protection from enzymatic hydrolysis. The intestinal hydrolysis of pro drug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides. No influence of lipid digestion process and increased drug loading capacity are the other advantages of SEDDS.

✓ Micronized drug delivery system.
✓ SEDDS are used for both liquid and solid dosage forms. E.g progesterone 12.
✓ High stability and reproducibility.
✓ Thermodynamic stability.
✓ Faster release rates and it improve the drug acceptance by consumers.
✓ Selective drug targeting toward a specific absorption window in the GI tract.
✓ Thus, for lipophilic drug compound that exhibit dissolution rate limitedabsorption.
✓ These systems may offer an improvement in the rate and extent of absorptionand result in more reproducible blood time profiles.[14,16,18,20,21]

CONCLUSION

From the above study on SEDDDS, we can concluded that the self emulsion drug delivery systems is promising approach for the development of formulations of drugs having poor aqueous solubility. The oral delivery of the hydrophobic drugs, improve by SEDDS. SEDDS will continue to enable novel application in drug delivery and to solve the problem regarding with delivery of poorly soluble drugs.

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