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A STATE OF THE ART REVIEW ON SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT: Solubility plays a vital role in achieving the therapeutic efficacy of a drug from a dosage form. Advances in molecular screening techniques for identification of potential drug molecules investigated an increased number of new pharmacologically active lipophilic compounds that are poorly water-soluble about 40% of new chemical entities have been discovered as poorly water-soluble. Numbers of technical strategies have been investigated for improving bioavailability like solid dispersions, cyclodextrins, micronization, surfactants, nanoparticles, lipids, permeation enhancers, *etc*. It is a great task for a pharmaceutical scientists to formulate oral dosage forms of these drug candidates with sufficient bioavailability. Among the various approaches to improve the oral bioavailability of these drug candidates, self-dispersing lipid formulations is one of the approaches to improve the bioavailability of lipophilic drugs. Self-dispersing lipid formulations is a very broad area that covers self-emulsifying drug delivery system (SEDDS), Self-micro emulsifying drug delivery system (SMEDDS), Self-nano emulsifying drug delivery system (SNEDDS) as carrier systems that have been developed.

INTRODUCTION: Poor bioavailability is a major challenge to formulate an oral dosage form. Poor aqueous solubility is one of the important underlying factors of bioavailability because a drug cannot be absorbed through the gastrointestinal tract unless it is in the solution state. Many chemical entities with significant and promising pharmacological effects suffer from poor aqueous solubility. It is stated earlier that over 30% of the most commonly marketed drug and nearly half of the new drug entities reaching to the formulation scientists are hydrophobic in nature or lacking required aqueous solubility.

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Self-emulsifying drug delivery system (SEDDS) is an isotropic mixture of lipid, surfactant, and co-surfactant, which forms a fine emulsion when it comes in contact with an aqueous medium with mild agitation. The oral route of drug administration is the preferred route for drug delivery in the human body due to the lower cost of production as compared to sterile dosage forms and high patient compliance since self-medication is possible. Poor aqueous solubility of drugs classified in biopharmaceutical classification systems (BCS) class II and IV show lower (fraction of dose absorbed << 1) and variable bioavailability after oral administration.

Around 70% of the new drugs invented show poor aqueous solubility, and this may be due to the shift of drug discovery processed from synthesis by trial and error-based approach to computer-aided drug design [1, 2].

Rapid first pass metabolism (RFPM), P-gp efflux, and presystemic clearance of drugs are also major causes for poor oral bioavailability [1, 3]. Several approaches have been adopted to improve the drug solubility and absorption such as modification of crystal habit, reduction of particle size, solid dispersions, solid solutions, salt formation, and miscellaneous methods, including supercritical fluid process and use of surfactant, solubilizers, cosolvency, hydrotrophy, and novel excipients as adjuvant to increase solubility.

Lipids can have formulated into oily solution, emulsion, microemulsion, SEDDS, Solid lipid nanoparticles *etc*. [4] SEDDS contains oils as well as surfactants and co-surfactants/co-solvents which do not allow drug precipitation after administration and drug may absorbed along with oil by lymphatic route which may help to overcome Rapid first-pass metabolism. Thus, SEDDS gives a reproducible blood concentration-time profile for lipophilic drugs. Further, it is widely accepted technique due to ease of formulation and scalability [2, 5, 6].

The potential of SEDDS for lipophilic compound was well understood long ago with the introduction of cyclosporine A by the pharmaceutical company, Sandoz (Germany) in the microemulsion form. For the lipophilic compounds which exhibit dissolution rate-limited absorption, SEDDS is gaining popularity to formulation scientists in order to render a reproducible drug–plasma concentration profile after oral administration since the early 90s.

Applications:

- The system has the ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation.
- SEDDSs present drugs in small droplet size and well-proportioned distribution and increase the dissolution and permeability.
- Selective targeting of the drug(s) toward a specific absorption window in GIT.
- Protection of drug(s) from the hostile environment in the gut.
- Control of delivery profiles.
- Reduced variability, including food effects.
- Protective of the sensitive drug substance.

Mechanism of SEDDS: Lipid-based formulations for oral delivery show a lot of diversity ranging from ‘simple oil solutions’ at lower side to complex ‘surfactant, cosurfactant or co-solubilizer and oil mixtures’ at the upper extreme. LBDDS can be modified greatly according to the need by changing their components as well as the concentration of these excipients, making them feasible for both hydrophilic and hydrophobic drugs. Their mechanism of enhancing bioavailability includes extended retention time in the stomach, change in the physical barrier, changes in the biochemical barrier, improved solubilization, decreased drug metabolism and stimulation of lymphatic transport. With time, these systems have been geared up to micro and nano scales resulting in their improved therapeutic potential for BCS class II, IV drugs. No single theory explains all aspects of microemulsion formation. Schulman *et al*., considered that the spontaneous formation of microemulsion droplets was due to the formation of a complex film at the oil-water interface by the surfactant and co-surfactant.

Thermodynamic theory of the formation of micro-emulsion explains that emulsification occurs when the entropy changes that favor dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The free energy in the micro-emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by the equation:

$$\Delta G = \Sigma N_{Л} r2\sigma$$

Where ΔG is the free energy associated with the process (ignoring the free energy of the mixing). N is the number of droplets of radius r, and σ are presented the interfacial energy. With time, the two phases of the emulsion tend to separate to reduce the interfacial area, and subsequently, the free energy of the system decreases. Therefore, the emulsion resulting from aqueous dilution is stabilized by conventional emulsifying agents, which forms a monolayer around the emulsion droplets, and hence, reduces the interfacial energy, as well as providing a barrier to prevent coalescence [7]. Self-emulsification depends on the nature of the oil and surfactant, the concentration of surfactant, the temperature at which self-emulsification occurs.

Biopharmaceutical Aspects: The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed, and the interested reader is directed to these references for further details [8, 9]. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability via a number via of potential mechanisms, including:

- **Alterations (Reduction) in Gastric Transit:** Thereby, slowing delivery to the absorption site and increasing the time available for dissolution [10].
- **Increase in Effective Luminal Drug Solubility:** The presence of lipids in the GI tract stimulates an increase in the secretion of bile salts (BS) and endogenous biliary lipids including phospholipid (PL) and cholesterol (CH), leading to the formation of BS/PL/CH intestinal mixed micelles and an increase in the solubilization capacity of the GI tract. However, intercalation of administered (exogenous) lipids into these BS structures either directly (if sufficiently polar), or secondary to digestion, leads to swelling of the micellar structures and a further increase in solubilization capacity.
- **Stimulation of Intestinal Lymphatic Transport:** For highly lipophilic drugs, lipids may enhance the extent of lymphatic transport and increase bioavailability directly or indirectly *via* a reduction in first-pass metabolism [11, 12].
- **Changes in the Biochemical Barrier Function of the GI Tract:** It is clear that certain lipids and surfactants may attenuate the activity of intestinal efflux transporters, as indicated by the p- glycoprotein efflux pump, and may also reduce the extent of enterocyte based metabolism [13, 14].
- **Changes in the Physical Barrier Function of the GI Tract:** Various combinations of lipids, lipid digestion products, and surfactants have been shown to have permeability enhancing properties. For the most part, however, passive intestinal permeability is not thought to be a major barrier to the bioavailability of the majority of poorly water-soluble, and in particular, lipophilic drugs.
- **Effect of Oils on the Absorption:** A SES also improves the reproducibility of the plasma level time profile. Various physiological mechanisms have been proposed to explain the effect of oils on the absorption of water-insoluble compounds, including altered gastrointestinal motility, increased bile flow and drug solubilization, increased mucosal permeability, enhanced mesenteric lymph flow, and increased lymphatic absorption of water-insoluble drugs and bioavailability also increased of the hydrophobic compound.

Limitations of SEDDS:

- Chemical instabilities of drug and high surfactant concentrations.
- A large amount of surfactant in self-emulsifying formulations (30-60% w/w) irritates GIT.
- Moreover, volatile co-solvent in the conventional self-emulsifying formulations are known to migrate into the shells of soft or hard gelatine capsule, resulting in the precipitation of the lipophilic drug [15].

Drug Properties Suitable for SEDDS:

- Bioavailability should below so as to enhance solubility.
- Dose should not be so high.
- Drug should be oil soluble.
- High melting point drug is poorly suited to SEDDS, lipophilic drugs with a low melting point less than 150 °C are often soluble in oils.
- log p-value should be high. (>2).
- High solubility in long-chain triglycerides for lymphatic transport absorption.

The self-emulsifying process depends on the nature of the oil and surfactant, the concentration of surfactant, the temperature at which self-emulsification occurs.

Excipients Used in SEDDS:
Lipids:

- Oils can solubilize the lipophilic drug in a specific amount. It is the most important

excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported *via* the intestinal lymphatic system, thereby increasing absorption from the GI tract.

Oil (sometimes a combination of different oils) with maximum ability to solubilize a specific drug usually is chosen as a lipid component to form SEDDS, showed [16] that the SEDDS with the lowest oil solubility resulted in highest bioavailability, which indicates that high solubility of the drug may not always be a good optimization parameter for better *in-vivo* performance and should not be used alone.

- Among the lipids used in SEDDS, long-chain fatty acids are converted to triglyceride by re-esterification in the small intestine and incorporated into chylomicron, a large lipoprotein, followed by secretion into the lymph vessel by exocytosis.

- Both long and medium-chain triglyceride (LCT and MCT) oils with different degrees of saturation have been used for the design of self-emulsifying formulations for getting pharmacologically stable emulsions.

- Furthermore, edible oils, which could represent the logical and preferred lipid excipients choice for the development of SMEDDS, are not frequently selected due to their poor ability to dissolve large amounts of lipophilic drugs.

- Modified or hydrolyzed vegetable oils have been widely used since these excipients form good emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties.

- They offer formulative and physiological advantages, and their degradation products resemble the natural end products of intestinal digestion.

- Lipids are generally of digestible and non-digestible. Mostly used lipids are digestible because these are more water-soluble than the parent lipids, and these can be solubilized within bile salt mixed micelles.

- The non-digestible lipids, when administered, they remain in the lumen and can decrease drug absorption by holding a fraction of the co-administered drug.

- Other than these novel semisynthetic medium-chain derivatives, which can be defined as amphiphilic compounds with surfactant properties, are progressively and effectively replacing the regular medium-chain triglyceride oils in the SMEDDS. As carbon chains increases in triglycerides, the melting point also increases. Generally, triglycerides are of mainly three types. 1) Short-chain triglycerides (SCT) 2) Medium-chain triglycerides (MCT) 3) Long-chain triglycerides (LCT). The mostly used triglycerides are medium-chain triglycerides and long-chain triglycerides.

Medium Chain Triglycerides and Related Esters:

- Lipids that have fatty acid chains of 6-12 carbons are categorized as MCTs. MCTs are the most common choice of oil for SMEDDS as they are resistant to oxidation and possess high solvent capacity compared to LCT because of their highly effective concentration of ester group.

- Drug substances should possess minimum solubility of 50 mg/ml in LCTs for lymphatic absorption. Upon digestion, products of short and medium-chain triglycerides are directed towards portal vein, whereas chylomicrons formed from LCTs triggers lymphatic transport. Moderately hydrophobic drug substances, on the other hand, cannot be formulated into simple oil solutions as their solubility is limited. In such cases, SMEDDS is a promising alternative where the drug solubility in the oil will be enhanced due to micro emulsification of oil by surfactants.

- It is well accepted that oils with long hydrocarbon chains (high molecular volume) such as soybean oil, castor oil are difficult to micro emulsify compared to

MCT (low molecular volume) such as capmul MCM and Miglyol.

- However, the solubilizing capacity of oil for lipophilic moiety increases with chain length (hydrophobic portion) of the oil. Hence the selection of oil is a compromise between the solubilizing potential and ability to facilitate the formation of micro-emulsion.

- Malcolmson *et al*., studied the solubility of testosterone propionate in various oils for the formulation of O/W microemulsion and concluded that oils with larger molecular volume such as triglycerides show superior solubility than the corresponding micellar solution containing only surfactants without oil [17, 18].

- Enhancement of drug solubility in SMEDDS not only relies on the solubility of the drug in the oil but also on the surfactant(s). For instance, ethyl butyrate, small molecular volume oil, has shown higher solubility for testosterone propionate but its ME formulation has only improved the solubility slightly than the corresponding micellar solution.

- On the contrary, Miglyol 812, which is a larger molecular volume oil, has shown improved solubilization in the ME formulation though the solubility of testosterone propionate is less in the individual components compared to ethyl butyrate.

Advantages of Medium Chain Triglyceride (MCT):

1. Digestible
2. Greater fluidity
3. Increase solubility
4. Good emulsifying property
5. Minimizes oxidation
6. Increase drug absorption
7. Positive effect on the bioavailability
8. No access to the lymphatic system

Examples: Pumpkin seed oil, Grapeseed oil, Lemon oil, Turmeric oil, Neem oil, Eucalyptus oil, Cottonseed oil, Soybean oil, Corn oil, Sunflower oil, Castor oil, Radish seed oil, Copaiba oil, Perilla seed oil, Turmeric leaf oil, Turmeric oil, Catnip oil, Imwitor 988, Imwitor 308, Capmul MCM, *etc*.

Long Chain Triglycerides:

- Lipids that have fatty acid chains of 14-20 carbons are categorized as LCTs. Fixed oils, *i.e.*, vegetable oils, contain a mixture of glyceride esters of unsaturated long-chain fatty acids. These are considered as safe as they are commonly present in daily food and are easily digestible.

- Large hydrophobic portion of triglycerides is responsible for their high solvent capacity for lipophilic moieties.

- Though it is difficult to micro emulsify, some marketed formulations such as Neoral® (composed of olive oil which, has shown superior oral bioavailability) and Topicaine® gel (composed of Jojoba oil for transdermal application) have been successfully practicing the micro emulsification of LCTs.

- Further, highly hydrophobic drug substances are easily soluble in vegetable oils and can easily be formulated as simple oil solutions that are readily emulsified in the gut. However, most conventional hydrophobic drug substances do not exhibit superior solubility in LCT [19,] such as vegetable oil.

Advantages of Long-Chain Triglyceride (LCT):

1. Vegetable source
2. Enhance the lymphatic pathways
3. Safe for the use
4. Increase bioavailability

e.g., Madhuca oil, Jojoba oil, Olive oil, Corn oil, *etc*.

Drug Solubility in Lipid:

- Oil component alters the solubility of the drug in SMEDDS by penetrating into the hydrophobic portion of the surfactant monolayer. Extent of oil penetration varies and depends on the molecular volume, polarity, size, and shape of the oil molecule.

- Overall, drug solubility in SMEDDS is always higher than the solubility of the drug in individual excipients that combine to form SMEDDS. However, such higher solubility considerably depends on the solubility of the drug in the oil phase, interfacial locus of the drug, and drug-surfactant interactions at the interface.
- In light scattering experiments, it was observed that oils with small molecular volume act like co-surfactants and penetrate into the surfactant monolayer. This forms thinner polyoxyethylene chains near the hydrophobic core of the micelle, disrupting the main locus of the drug solubilization due to which a higher solubility of drug is not observed.
- Large molecular volume oils, however, form a distinct core and do not penetrate effectively into the surfactant monolayer. The locus of drug solubilization was found to be affected by the microstructure and solubility of the drug in the excipients.
- *E.g.*: The locus of drug solubilization was found to be at the interface of micelle for phytosterols, whereas the same for cholesterol was found to be between the hydrophobic head groups of surfactant molecules. This is attributed to altered side-chain flexibility of phytosterol due to the additional substitution of alkyl side chain compared to cholesterol [20.]
- In addition to molecular volume and polarity of the oil, drug solubility in oil is affected by the physicochemical properties of the drug molecule itself. Consideration of BCS classification and Lipinski's rule of 5 for the selection of drugs is only useful during initial screening stages.
- As per BCS classification, some of the acidic drugs are listed in Class II despite having good absorption and disposition as they do not satisfy the requirement of higher solubility at low pH values. Lipinski's rule of 5, on the other hand, holds good only when the drug is not a substrate for the active transporter.
- This suggests that aqueous solubility and log P alone are not sufficient to predict the solubility of the drug in the oil. This further indicates that the solubility of any two drugs with similar log P would not be the same due to their different physicochemical properties.
- To demonstrate this, a study was conducted in with two antihypertensive drugs having close partition coefficient (log P) values, different aqueous solubility and varying physicochemical properties. Candesartan cilexetil is hydrophobic and has log P value of 7.3, molecular weight 610.66 g/mol with a polar surface area 135.77 whereas, valsartan is slightly soluble in aqueous phase with log P value of 5.3, molecular weight 434.53 g/mol with a polar surface area 103.48 (logP and polar surface area were calculated using chembiodraw ultra 11.0). Unlike candesartan cilexetil, valsartan exhibits pH-dependent solubility [21.]

Surfactants: The second obligatory component in SEDDS is surfactants, which are amphiphilic molecules with a hydrophilic head and hydrophobic tail. These surfactants are added to SEDDS formulation due to their ability to reduce the surface tension and form monolayer between the oil and aqueous phase.

- Stabilization of the oil droplets will be happened, as a result of the localization of the surfactant molecules at the oil-water interface. The surfactants used in these formulations are known to improve the bioavailability by various mechanisms, including; improved drug dissolution, increased intestinal epithelial permeability, increased tight junction permeability, and decreased/inhibited p-glycoprotein drug efflux.
- The maximum solubility of the drug in surfactant and the hydrophilic-lipophilic balance (HLB) are two major considerations that must be taken when choosing surfactant in SEDDS. Both HLB values and the concentration of surfactants have a major impact on the emulsion droplet size.

The droplet size of the emulsions decreases and then increases with increasing surfactant concentration because at the beginning, the amount of adsorbed surfactant around the oil-water interface of a droplet increases, resulting in decreasing the interfacial tension of the system and form fine droplets.

- When the concentration of surfactant increases, excess water penetrates into the bulk oil causing massive interfacial disruption and ejection of droplets into the bulk aqueous phase.

- Property of surfactants such as HLB value, cloud point, viscosity, and affinity for oil phase has a strong influence on the emulsification process and droplet size, and by this, we can conclude that the concentration of surfactants in SEDDS should be in the range of 30-60% w/w.

- The HLB value of selected surfactants reflects the stability of the system and can be obtained when the HLBs of surfactant and oil are similar. The combination of hydrophilic and lipophilic non-ionic surfactants is able to build highly structured emulsions.

- *E.g.* Tween 80, hydrophilic surfactant with HLB value of 15 and span 80, lipophilic surfactant with HLB value 4.3. The combination of these two surfactants along with cosurfactants forms a stable emulsion.

- The presence of higher quantity of hydrophilic surfactants also leads to greater drug precipitation. For this supersaturated SNEDDS containing hydrophilic precipi-tation inhibitors have been introduced successfully.

- *E.g.*, HPMC, Sodium carboxy methyl cellulose, Methylcellulose polymers are examples of precipitation inhibitor. Surfactants with very low HLB value will dissolve in the oil phase, and the surfactant with high HLB value dissolves in water that enables them to function together well enough to have a stronger effect than surfactant and mixture having low HLB value.

- Surfactant molecules may be classified based on the nature of the hydrophilic group within the molecule. The four main groups of surfactants are defined as follows:

  - ✓ Anionic surfactants
  - ✓ Cationic surfactants
  - ✓ Ampholytic surfactants
  - ✓ Non-ionic surfactants

- **Non-ionic Surfactants:** The non-ionic surfactants are the water-soluble and insoluble type with relatively high HLB values are the most widely recommended surfactant to be used in the SEDDS due to their less toxicity and possess low CMC, such as Sorbitan ester and Ethoxyl esters of fatty acids and Lecithin with HLB values ranging between 4 and 15.

  E.g., Brij 30, Labrafac CM10, Tween 20, Tween 80, Cremophor RH40, Pluronic L64, and Emulphor E620, Vitamin ETPGS.

- Some non-ionic surfactants like Cremophore EL, Cremophore RH40, Span, Tween are reported to inhibit P-gp (P-glycoprotein), which is one of the commonly known efflux transporters. The best matches for the formulation are non- ionic surfactants which are

  - ✓ High HLB value
  - ✓ Less toxic than ionic
  - ✓ Greater emulsion stability

- Even though some surfactants obtained from same parent chain, they influence the particle size and bioavailability. For example, Cremophor EL (polyoxyl 35 castor oil) is a pale yellow oily liquid.

- The particle size and size distribution of emulsions emulsified by cremophor EL tend to be smaller and narrow than those emulsified by cremophor RH 40. Other than fine globule formation, inhibition of the efflux transporter by surfactants is considered as a contributing factor to

enhance bioavailability by minimizing the chance of efflux back of the compound to the intestinal lumen potential effects of excipients show different effects on the intestinal wall. For example, polysorbates like Twee 20, Tween 80 show the inhibitory effect on CYP3A and P-Glycoprotein and like this polyoxyl 35 castor oil (cremophor RH and EL 40) shows the same inhibitory effect. The inhibitory action involves the inhibition of drug metabolism and efflux effect of P-glycoprotein.

Advantages of Surfactants:

- Give the self-emulsification property.
- Solubilizes the hydrophobic drug.
- Dissolution rate can be improved.
- *In-vivo* Inhibitory effect on drug precipitation.
- Improves permeability by opening the tight junctions.
- Stabilizes the micro emulsion system.

Co-solvents:

- The production of an optimum SEDDS requires relatively high concentrations (generally more than 30% w/w) of surfactants; thus, the concentration of surfactant can be reduced by incorporation of co-surfactant.

- Role of the cosurfactant, together with the surfactant, is to lower the interfacial tension to a very small, even transient negative value. At this value, the interface would expand to form finely dispersed droplets, and subsequently, adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again.

- This process is known as 'spontaneous emulsification' forms the microemulsion. However, the use of cosurfactant in self-emulsifying systems is not mandatory for many non-ionic surfactants. The selection of surfactant and co-surfactant is crucial not only to the formation of SEDDS but also to solubilization of the drug in the SEDDS.

- Organic solvents suitable for oral administration (ethanol, propylene glycol (PG), polyethylene glycol (PEG), *etc*.) may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as cosurfactant in the self-emulsifying drug delivery systems.

- Indeed, such systems may exhibit some advantages over the previous formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying formulations are known to migrate into the shells of soft gelatine or hard sealed gelatine capsules resulting in the precipitation of the lipophilic drug. On the other hand, the lipophilic drug dissolution ability of the alcohol-free formulation may be limited. Hence, the proper choice has to be made during the selection of components [22].

- In SMEDDS, generally co-surfactant of HLB value 10-14 is used. Co-surfactant mainly help increase drug load capacity. The addition of co-surfactant reduces the chances of variability and local irritancy caused by the surfactants by increasing the interfacial fluidity. Commonly used co-surfactants include ethanol, propylene glycol, and other newer co-surfactants such as transcutol P and Glycofurol, *etc*.

Properties of Cosurfactants:

- They should be hydrophilic in nature.
- Access the entry of water into the formulation.
- Assist the dispersion process.
- Imparts the flexibility to the interface, the range of co-solvents and co-surfactants should be in 20-50% w/w of the formulation.

Other Excipients Added to SEDDS Formulations:

Viscosity Enhancers: These are components that are added to self-emulsifying drug delivery systems to alter the viscosity of the formulations. Some examples of include; Tragacanth, Beeswax, Acetyl alcohol, stearic acid.

Antioxidants:

- In SEDDS formulations, antioxidants of lipophilic nature are added to stabilize the oil phase of the formulations. Examples include; Tocopherol, Ascorbic acid, Propyl gallate.

Polymers:

- Inert polymers which are non-ionizable at physiological pH present 5% to 40% w/w are able to form a matrix. When added to SEDDS formulation, it prevents precipitation by formulating super saturable SEDDS. Polymers include; hydroxypropyl methylcellulose, ethylcellulose, polyvinyl pyrrolidine, sodium carboxymethyl cellulose, methylcellulose.

- Hydrophobic HPMC can also be used, and in fact hydrophobic and high molecular weight HPMC polymers are more effective in maintaining the super saturable state. Some drugs precipitate in amorphous form and show notable fasters rates of dissolution after precipitation when tested *in-vitro*.

- It implies that precipitation of drugs showing such behavior, leads to increase the bioavailability, remains to be illuminated and clarified *in-vivo*.

Enzyme Inhibitors: If the therapeutic agent is subject to enzymatic degradation, enzyme inhibitors can be added to the composition of SMEDDS. Enzyme inhibitors are;

1. Inhibitors that are not based on amino acids. *e.g.* P-amino benzamidine, FK-448, Cosmo-statmysylate, sodium glycolate.

2. Amino acids and modified amino acids e.g. amino boronine derivatives and n-acetyl-cysteine.
3. Peptides and modified peptides *e.g.* Bacitracin, antipain, leupeptin, amastatin.

4. Polypeptide protease inhibitors, *e.g.,* Aprotinin, Bowman-Birk inhibitor, Soybean trypsin inhibitor, Chicken egg white trypsin inhibitor.

Complexing agent, *e.g.,* EDTA, EGTA, 1, 10 phenanthroline, Hydroxycholine

Process of Self-Emulsification:

Self-Nano Emulsifying Drug Delivery System (SNEDDS): SNEDDS are Nano-emulsions formed by SEDDS. They are heterogeneous dispersions of two immiscible liquids (oil-in-water [O/W] or water-in-oil [W/O]) having a mean droplet size in the nanometric scale (typically 20–200 nm), regardless of method of preparation. This is particularly important for drugs for increasing the solubility such as simvastatin, atorvastatin [23].

Self-Micro Emulsifying Drug Delivery System (SMEDDS): SMEDDS are micro-emulsions formed by the SEDDS. It is thermodynamically stable and forms optically transparent emulsion. The major difference between micro-emulsions and common emulsions is mainly due to the particle size of droplets. The size of the droplets of common emulsion ranges between 0.2 and 10 μm, and that of the droplets of microemulsion formed by the SMEDDS generally ranges between 2 and 100 nm. Since the particle size is small, the total surface area for absorption and dispersion is significantly larger than that of solid dosage form, and it can easily penetrate the gastrointestinal tract and be absorbed. The bioavailability of drugs is therefore improved [19].

Method of Preparation:

Formulation:

Screening of Excipients:

Solubility Studies:

Method: Shake flask method in which the drug is solubilized with the excipients (excess amount) 0.5gm each of the solvent. It is shaken for the 48 h a water bath shaker at room temperature. The solution is then centrifuged for 15 min. Then, the supernatant is filtered (0.45 um). Then the drug content will be determined by HPLC.

1. Screening of Surfactants and Co-surfactants for their Self-Emulsification Ability: Equal proportions of oil and surfactants (0.3 gm) are homogenized for 2 min and then warmed for 30 sec (40-45 °C). Then the 50 mg of the prepared isotropic mixture is added to distilled water and allowed to stand for 2 h. The prepared microemulsion is filtered and tested for clarity,

turbidity, and % transmittance (wavelength-638 nm). If the resultant % transmittance is high, then the emulsification efficiency will be high, low flask inversions, clear emulsion if formed, then those surfactants and co-surfactants are selected.

Construction of Pseudo Ternary Phase Diagram: Co surfactant + surfactant = Smix

- It helps in deciding the ratio of oil, surfactant and cosurfactant to be formulated in the SMEDDS by pseudo ternary diagram.
- The ratio of oil, surfactant, and co-surfactant are to be added in vials with 5% w/w of water. They are centrifuged for 2-3 min for phase separation. They are incubated for 48 h (25 °C). The vials are shaken, and the ratio of formulation, which shows clear and isotropic mixture, is select. Preparation The selected hydrophobic drug, oil, surfactant, and cosurfactant are vortexed for 5-10 min in a magnetic stirrer. The prepared emulsion is to be placed in an oven at 50 °C for 1 h. Then it is checked for turbidity. If required, vortex for 48 h until a clear solution obtained or heat it.
- Pseudo ternary phase diagrams are constructed with the selected excipients by titration method and by keeping the ratio of any two of the four components constant (usually surfactant and co-surfactant).
- This is mixed with the required volume of the third phase (usually oil) in different ratios. Each individual mixture is titrated with the fourth component usually water in incremental amounts and tested for the clarity, flowability time for self-emulsification, and dispersibility.
- Compositions, which form clear solutions, are denoted by suitable symbols in the ternary diagram, joined, and the area indicates the existing microemulsion area. Wider area indicates the good self-emulsification capacity.
- From pseudo ternary phase diagram, the formulation is optimized mainly based on globule size, self-emulsification time. SMEDDS can be easily prepared in a single step by dissolving the drug in the selected composition of excipients by simple mixing with no critical steps.
- Pseudo ternary phase diagram is used to map the optimal range for three key excipients according to the resulting droplet size following self emulsification.
- The formulation is generally prepared by mixing lipids, surfactants, co-surfactants, and drugs. If it needs to be formulated into a semi-solid or solid dosage form, then it will be mixed with solid carriers.
- The methods are used for the preparation of solid SEDDS such as spray drying methods, adsorption to solid carriers, melt granulation, and melt extrusion sphero-nization. The spray drying method is generally used to convert liquid formulation into the solid formulation.
- Solubilization of the mixture is done before spray drying. Solubilised liquid formulation is then atomized into a spray of droplets. Droplets are then introduced into a drying chamber, where the volatile phase is evaporated.
- The design of the drying chamber is selected according to the drying characteristic of the product and powder specification. Then the dried powder is prepared into a tablet. Melt granulation technique is generally used for the formulation of the SEDDS tablet.
- Capsule filling with liquid and semisolid self-emulsifying formulations is alone done. For semisolid formulations, it is a four-step process. In first step we provide heat to the semisolid excipients to at least 20 °C or above its melting point. In the second step active substances are incorporated in it with stirring. The next step involves capsule filling with the melt cooling to room temperature.
- The last step which is used for liquid formulations involves capsules filling with the formulation, then the body and cap of the capsule is sealed either by banding or by micro spray sealing.

Different Dosage Forms of SEDDS:

- Dry emulsions.
- Self-emulsifying capsules.
- Self-emulsifying sustained/controlled-release tablets.
- Self-emulsifying sustained/controlled-release pellets.
- Self-emulsifying solid dispersions.
- Self-emulsifying sustained-release micro-spheres.
- Self-emulsifying nanoparticles.
- Self-emulsifying suppositories.
- Self-emulsifying implant.

Need of SEDDS: self-emulsifying formulation spread readily in gastrointestinal tract (GIT), and GI motility of the stomach and the intestine provide the necessary agitation for self-emulsion. SEDDS are a promising approach for oral delivery of poorly water-soluble compounds. It can be achieved pre-dissolving the compounds in suitable solvents and fill the formulations into capsules. Pre-dissolving the compounds overcome the initial rate-limiting step of particulate dissolution in the aqueous environment within the GI tract [24].

Characteristics of SEDDS:

- They are able to self emulsify rapidly in GI fluids & under the influence of peristaltic and other movements of GIT and form a fine o/w emulsion.
- They can effectively incorporate drugs (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms like suspension, emulsion, tablets, pellets, and suppositories.
- They require a lower dose of the drug with respect to conventional dosage forms [25].

Factors Affecting to SEEDS:

Drug Dose: Drugs, which are administered at very high dose, are not suitable for SMEDDS unless they exhibit extremely good solubility in at least one of the components of SMEDDS, preferably lipophilic phase. The drugs exhibit limited solubility in water and lipids (typically log P values of approximately 2) are most difficult to deliver by SMEDDS.

Drug Solubility in Oil Phase: The ability of SMEDDS to maintain the drug in solubilised form is generally influenced by the solubility of the drug in oily phase. If the surfactant or co-surfactant is contributing to a greater extent of drug solubilization, then there could be a risk of precipitation, as dilution of SMEDDS will lead to lowering of solvent capacity of surfactant or co surfactant.

Equilibrium Solubility Measurement: It can be carried out to anticipate potential cases of precipitation in the gut. However, crystallization could be slow in a solubilizing environment of the gut. Poutons study reveals that such formulation can take up to 5 days to reach equilibrium and that the drug can remain in a supersaturated state up to 24 h after the initial emulsification event.

Polarity of Lipid Phase: The polarity of lipid phase is one of the factors that govern the release from the microemulsion. HLB, chain length, and degree of unsaturation of fatty acid, the molecular weight of the lipophilic portion, and concentration of the emulsifier govern the polarity of droplets. In fact, the polarity reflects the affinity of the drug for oil and /or water and the type of forces involved. The high polarity will promote the rapid rate of release of the drug into the aqueous phase. This is confirmed by the observation of Sang-Cheol *et al*., who observed that the rate of release of Idebenone from SMEDDS is dependent upon the polarity of oil phase used. The highest release was obtained with the formulation that had an oily phase with the highest polarity.

Charge of Emulsion Droplets: Multiple physiological studies have proved that the apical potential of absorptive cells, as well as that of all other cells in the body, is negatively charged with respect to the mucosal solution in the lumen54. Gershanik and Benita have shown that positively charged emulsion droplets formed by adding oleylamine (OA) to appropriate SEDDS undergo electrostatic interaction with the CaCO-2 monolayer and the mucosal surface of the everted rat intestine. This formulation enhanced the oral bioavailability of progesterone in young rats.

Benzoic acid had a dual function on the SEDDS; it could improve the self-emulsifying performance of self-emulsifying oily formulations (SEOFs) and self-micro emulsifying oily formulations (SMEOFs) in 0.1N HCl due to formation of a positively charged emulsion.

Evaluation of SEDDS: [23-26] A number of tests are carried out for characterization and evaluation of SEDDS.

Thermodynamic Stability Studies: The physical stability of a lipid-based formulation is also crucial to its performance, which can be adversely affected by precipitation of the drug in the excipient matrix. In addition, poor formulation physical stability can lead to phase separation of the excipient, affecting not only formulation performance, but visual appearance as well.

In addition, incompatibilities between the formulation and the gelatine capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of the drug.

1. Heating cooling cycle six cycles between refrigerator temperature (4 °C) and 45 °C with storage at each temperature of not less than 48 h is studied. Those formulations, which are stable at these temperatures, are subjected to centrifugation test.

2. Centrifugation passed formulations are centrifuged thaw cycles between 21 °C and ± 25 °C with storage at each temperature for not less than 48 h is done at 3500 rpm for 30 min. Those formulations that do not show any phase separation are taken for the freeze-thaw stress test.

3. Freeze-thaw cycle three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility Test: The efficiency of self-emulsification of oral nano or microemulsion is assessed using a standard USP XXII dissolution apparatus II. One milliliter of each formulation was added to 500 mL of water at 37 ± 0.5 °C. A standard stainless steel dissolution paddle rotating at 50 rpm provided gentle agitation. The *in-vitro* performance of the formulations is visually assessed using the following grading system:

Grade A: Rapidly forming (within 1 min) Nano emulsion, having a clear or bluish appearance.

Grade B: Rapidly forming, slightly less clear emulsion, having a bluish-white appearance.

Grade C: Fines milky emulsion that formed within 2 min.

Grade D: Dull, greyish white emulsion having a slightly oily appearance that is slow to emulsify (longer than 2 min).

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface. Grade A and Grade B formulation will remain as Nano emulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

Turbidimetric Evaluation: Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. A fixed quantity of Self emulsifying system is added to a fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on the magnetic plate at ambient temperature, and the increase in turbidity is measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification).

Zeta Potential Measurement: This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to the presence of free fatty acids. The optimum zeta potential value for forming the stable self nanoemulsions is ±25. Zeta potential value should be negative mostly; the negative value indicates the high drug loading capacity.

Viscosity Determination: The SEDDS system is generally administered in soft gelatine or hard gelatine capsules. So, it can be easily pourable into capsules, and such a system should not too turbidimetric evaluation nepheloturbidimetric evaluation is done to monitor the growth of emulsification. A fixed quantity of self-emulsifying system is added to a fixed quantity of suitable medium (0.1N hydrochloric acid) under continuous stirring (50 rpm) on the magnetic plate at ambient temperature, and the increase in turbidity is

measured using a turbidimeter. However, since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity (rate of emulsification).

Size Analysis Particle Size Measurements: The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to the Brownian motion of the particles) using a Zeta sizer able to measure sizes between 10 and 5000 nm. Light scattering is monitored at 25 °C at a 90° angle, after external standardization with spherical polystyrene beads. The nanometric size range of the particle is retained even after 100 times dilution with water, which proves the system's compatibility with excess water.

Refractive Index and Percent Transmittance: Refractive index and percent transmittance proved the transparency of formulation. The refractive index of the system is measured by a refractometer by placing a drop of solution on the slide, and it compares with water (1.333). The percent transmittance of the system is measured at a particular wavelength using UV-Spectrophotometer, keeping distilled water as blank. If the refractive index of the system is similar to the refractive index of water (1.333) and formulation has percent transmittance > 99 percent, then formulation has transparent nature.

Electro Conductivity Study: The SEDD system contains an ionic or non-ionic surfactant, oil, and water. So, this test is used to measure the electro-conductive nature of the system. The electroconductivity of the resultant system is measured by electro conductometer.

***In-vitro* Diffusion Study:** *In-vitro* diffusion study is performed to study the release behavior of formulation from the liquid crystalline phase around the droplet using the dialysis technique.

Drug Content: Drug from pre-weighed SEDDS is extracted by dissolving in a suitable solvent. The drug content in the solvent extract was analyzed by a suitable analytical method against the standard solvent solution of the drug.

Polydispersity Index: This is used to identify the charge of droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to the presence of free acids. The optimum polydispersity value should be less, maintained within the range of 0.1-0.3 for best formulation.

Cloud Point Determination: The prepared formulation (0.5 ml) is added to the distilled water (50 ml) are to be placed on a water bath. The temperature is to be raised at the rate of 0.5 °C /min then the emulsion is cooled till they become cloudy, and they are checked spectrophotometrically.

Phase Separation Study: 1ml sample of SMEDDS is taken with 5 ml 0.1N HCl in a glass tube. Then the buffer pH 6.8 and distilled water are added. They are altered for 3-4 times between 2 h.

Differential Scanning Colorimetry and NMR Techniques: DSC gives information about water, which is in a free-state and bound state. In NMR, Fourier transformed the pulsed gradient spin echo method (PGSE) PGSE-NMR.

Visual Evaluation: The prepared SMEDDS are dissolved in water, if the emulsion appears opaque or milky white, then it is micro-emulsion, and if it appears clear, isotopic and transparent, then it is micro-emulsion.

Freeze Thawing Method: The method in which the formulation is kept at -4 °C for freezing (24 h) and at 40 °C thawing (24 h) after that centrifuged for 3000RPM (5 min).

Transmission Electron Microscopy (TEM): Investigates the structures and morphology of microemulsion by dilution of SMEDDS.

Recent Techniques used for SEDDS:

1. Adsorption on Solid Carriers:

A. Physical Adsorption: These solid carriers have a property to absorb liquid/semisolid formulation as a self-emulsifying system (SES). It is a simple procedure, where SES is incorporated into a free-flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into a capsule or added to more excipient for compression into tablets. The above mixture was solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (Florite

TMRE); magnesium aluminum silicate (NeusilinTMUS2), and Silicon Dioxide.

B. Spray Drying: In this technique, first, the prepared formulation containing oil, surfactant, drug, solid carrier, *etc*., is sprayed into a drying chamber through a nozzle. The volatile vehicles first evaporate, leaving behind small solid particles. These particles are then filled into capsules or compressed into tablets.

2. Self-emulsifying Capsules: After administration of capsules containing conventional liquid self-emulsifying formulations, microemulsion droplets are formed and subsequently get dispersed in the GI tract to reach sites of absorption. Besides liquid filling, liquid self-emulsifying ingredients also can be filled into capsules in a solid or semisolid state obtained by adding solid carriers (adsorbents, polymers). Various researchers have converted liquid SEDDS to solid SEDDS and packed them in capsules.

3. Self-emulsifying Tablets: The liquid SEDDS are first adsorbed on to solid carriers and then compressed into tablets after adding tablet excipient. The newest advance in the research field of the self-emulsifying tablet is the self-emulsifying osmotic pump tablet, where the elementary osmotic pump system was chosen as the carrier of SES.

4. Self-emulsifying Beads: In an attempt to transform SES into a solid form with minimum amounts of solidifying excipients, the loading SEDDS into the microchannels of porous polystyrene beads (PPB) using the solvent evaporation method was studied. PPB with complex internal void structures is typically produced by copolymerizing styrene and divinylbenzene. They are inert, stable over a wide pH range, and to extreme conditions of temperature and humidity. This research concluded that PPB was potential carrier for solidification of SES, with sufficiently high SES to PPB ratios required to obtain solid form. Geometrical features, such as bead size and pore architecture of PPB, were found to govern the loading efficiency and in vitro drug release from SES-loaded PPB.

5. Self-emulsifying Liposphere: The poorly a water-soluble drug, piroxicam, was incorporated into self-emulsifying lipospheres consisting of a mixture of a homolipid from Capra hircus and Tween 65. Various solid self-emulsifying lipo-spheres were formulated, having different ratios of the homolipid and Tween 65 to contain piroxicam. The self-emulsifying lipospheres were evaluated using the following parameters: particle size, absolute drug content, and dissolution profile. The pharmacodynamics of the drug from the lipo-spheres was also evaluated using antinociceptive activity on albino mice. These lipospheres gave the best therapeutic effects.

6. Melt Granulation: Melt granulation is a process in which powder agglomeration is obtained through the addition of a binder that melts or softens at relatively low temperatures. As a 'one-step' operation, melt granulation offers several advantages compared with conventional wet granulation since liquid addition, and the subsequent drying phase is omitted. Moreover, it is also a good alternative to the use of a solvent. The melt granulation technique, also described as "Thermoplastic pelletization," is easily adaptable to lipid-based excipients that exhibit thermoplastic properties. A wide range of solid and semi-solid lipids can be used as a meltable binder for solid dispersions. Generally, lipids with a low HLB and high melting point are suitable for sustained release applications. Semi-solid excipients with high HLB, on the other hand, maybe used for immediate release and bioavailability enhancement.

Other lipid-based excipients evaluated for melt granulation to create solid SES include lecithin, partial glycerides, or polysorbates. The melt granulation process is usually used for adsorbing SES onto solid neutral carriers like silica and magnesium alumino meta-silicate. The main parameters that control the granulation process are the impeller speed, mixing time, binder particle size, and the viscosity of the binder.

7. Supercritical Fluid based Methods: Lipids may be used in supercritical fluid-based methods either for coating of drug particles or for producing solid dispersions. The coating process entails dispersing the drug particles as a powder in a supercritical fluid containing one or more dissolved coating materials. The solubility of the coating material is sustained initially by elevated pressure and temperature conditions.

The coating process is subsequently facilitated by a gradual reduction in pressure and temperature, leading to the reduced solubility of the energy or environmental concerns relating to the evaporation of solvents if applicable. The coating material in the supercritical fluid is allowing gradual deposition onto the drug particles to form a coating layer. The supercritical fluid of choice is supercritical carbon dioxide. The process for obtaining solid particles entails dissolving the drug and lipid-based excipients in an organic solvent such as methanol and then in a supercritical fluid, followed by lowering the temperature and pressure conditions to reduce their solubility in the fluid. Examples of lipid-based or lipid-related excipients that have been studied with this process for controlled-release applications include glyceryl tri myristate (Dynasan™ 114). The important considerations with this formulation technique are:

- ✓ The solubility of the formulation components in the supercritical fluid.
- ✓ The integrity stability of the active substance under the process conditions.
- ✓ Compared with other methods, it has one of the highest potentials for lipid Exposure and a relatively lower drug loading capacity so they are best suited for highly potent and low dose drugs.

8. Self-emulsifying Nanoparticles: Nanoparticle techniques have been used in the production of SE nanoparticles. The solvent injection is one of these techniques in which the lipid, surfactant, and drugs are melted together, then injected drop-wise into a stirred non-solvent. The resulting self-emulsifying nanoparticles are then obtained by filtration and dried. This approach produced nanoparticles of about 100 nm with a high drug loading efficiency of 74%. A second technique involves sonication emulsion-diffusion evaporation, which allowed the co-loading 5-fluorouracil and antisense epidermal growth factor receptor plasmids in the biodegradable nanoparticle.

The mixture of poly-lactide-co-glycolide and Carboxymethyl-chitosan exhibited an SE effect, without a surfactant stabilizer. A novel nanoparticle drug delivery system consisting of chitosan and glyceryl monooleate for the delivery of paclitaxel was developed with bioadhesive properties, and increased cellular association was prepared by the multiple emulsions (O/W/O) solvent evaporation method [9].

Self-emulsifying Suppositories: Some investigators have shown that SEDDS can increase not only GI adsorption but also rectal/vaginal adsorption. Glycyrrhizin was given by the oral route barely achieves therapeutic plasma concentrations, but satisfactory therapeutic levels for the treatment of chronic hepatic diseases can be achieved by the use of either vaginal or rectal SE suppositories.

9. Self-emulsifying Implants: Research into SE implants has greatly increased the use and application of S-SEDDS. As an example, 1, 3-bis (2-chloroethyl)-1-nitrosourea (Carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. Its effectiveness was hindered by its short half-life. In order to enhance its stability compared with its release from poly (d, l-lactide-co-glycolide) (PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl 40 hydrogenated castor oil) and Labrafil 1944 (polyglycolyzed glycerides). Then, the self-emulsified BCNU was fabricated into wafers with a flat and smooth surface by compression molding. Ultimately, SES increased the *in-vitro* half-life of BCNU up to 130 min compared with 45 min with intact BCNU. The copolymers having a bio-resorbable region, a hydrophilic region and at least two cross-linkable functional groups per polymer chain were developed, such copolymers exhibit SE properties without the requirement of an emulsifying agent. These copolymers can be used as good sealants for implantable prostheses [24, 25].

Future Aspects:

1. Self-emulsifying Solid Dispersions: Although solid dispersions could increase the dissolution rate and bioavailability of poorly water-soluble drugs, some manufacturing difficulties and stability problems existed [27]. Serajuddin pointed out that these difficulties could be surmounted by the use of SE excipients. These excipients have the potential to increase further the absorption of poorly water-soluble drugs relative to previously used PEG solid dispersions and may also be filled directly into hard gelatin capsules in the molten state, thus obviating the former requirement for milling and blending

before filling. SE excipients like Gelucire144/14, Gelucire1 50/02, Labrasol1, Transcutol, and TGPS (tocopherol polyethylene glycol 1000 succinate) have been widely used in the field.

2. Self-emulsifying Suppositories: Some investigators proved that SEDDS could increase not only GI adsorption but also rectal/vaginal adsorption [60]. Glycyrrhizin, which, by the oral route, barely achieves therapeutic plasma concentrations, can obtain satisfactory therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories [28]. The formulation included glycyrrhizin and a mixture of a C_6C_{18} fatty acid microgol ester.

3. Self-emulsifying Sustained/Controlled-Release Pellets: Pellets, as a multiple unit dosage forms, possess many advantages over conventional solid dosage forms, such as flexibility of manufacture, reducing intrasubject and intersubject variability of plasma profiles and minimizing the GI irritation without lowering the drug bioavailability. Thus, it is very appealing to combine the advantages of pellets with those of SEDDS by SE pellets. Serratoni *et al*., prepared SE controlled release pellets incorporating drugs into SES that enhanced their rate of release, and then by coating pellets with a water-insoluble polymer that reduced the rate of drug release [29, 30]. Pellets were prepared by extrusion/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained monodiglycerides and Polysorbate 80. There is another report that SE sustained release matrix pellets could be successfully formulated with glyceryl palmito-stearate (glucire 54/02) and glyceryl behenate (gelucire 70/02).

Advantages:

- Quick onset of action.
- Reduction in drug dose.
- Ease of manufacture and scale-up.
- Improvement in oral bioavailability.
- Intersubject and intrasubject variability and food effects.
- Ability to deliver peptides that are prone to enzymatic hydrolysis in the GIT.
- No influence of lipid digestion process.
- Increased drug loading capacity.

Disadvantages:

- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60% w/w).
- Volatile co-solvents in the conventional SMEDDS formulations are known to migrate into the shells of soft or hard gelatine capsules, resulting in the precipitation of the lipophilic drugs.
- Further development will be based on *in-vitro – in-vivo* correlations, and therefore different prototype lipid-based formulations need to be developed and tested in vivo in a suitable animal model
- High production cost.
- Low drug incompatibility.
- Drug leakage. So, it may allow for less drug loading.

CONCLUSION: Self-emulsifying drug delivery systems are actually mixtures of the drug, lipid phase, emulsifier and/or co-solvent. SEDDS are a promising approach for drugs with poor aqueous solubility and hence can be more useful for BCS Class II and IV drugs as upon administration. When the dosage form reaches G.I.T, the SEDDS system takes water from its surrounding environment and spontaneously forms oil in water emulsion, which disperses into fine droplets. The finer droplets provide higher surface areas for the drug to dissolve or permeate in the surrounding medium. SEDDS are generally prepared in liquid dosage forms, but solid SEDDS (tablets, capsules, beads, microspheres, etc.) are preferred due to ease in handling, transportation, and better stability.

Also, it avoids GI irritation and controlled, and sustained release of drug release is achievable. The absence of suitable *in-vitro* models explaining the state (whether dissolved or not) in G.I.T (*in-vivo*) for evaluation of SEDDS is major hurdles. Further, with solid SEDDS, compatibility, and interaction studies between the excipients such as adsorbent, capsule shell & formulation components can be carried out in order to effectively harness its potential for the benefit of mankind. The SEDDS should be suitably exploited to develop platform technologies for improving the bioavailability of BCS class II and IV drugs.

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REFERENCES:

1. Humberstone AJ and Charman WN: Lipid-based vehicles for the oral delivery of poorly 418 water soluble drugs, Adv Drug Deliv Rev 1997; 25: 103-28.
2. Aungst BJ: Intestinal permeation enhancers. J Pharm Sci 2000; 89: 429-42.
3. Kovvasu SP, Kunamaneni P, Joshi R and Betageri GV: Self-emulsifying drug delivery systems and their marketed products: a review. Asian Journal of Pharmaceutics 2019; 13(2): 73.
4. Bandivadekar M, Pancholi SS, Kaul-Ghanekar R, Choudhari A and Koppikar S: Self-micro emulsifying smaller molecular volume oil (Capmul MCM) using non-ionic surfactants: A delivery system for poorly water-soluble drug. Drug Dev Ind Pharm 2012; 38: 883-92.
5. Gunnam S: Formulation and evaluation of Self emulsifying drug delivery system of bosentan. Asian J Pharm 2018; 12: S822-33.
6. Constantinides PP: Lipid microemulsions for improving drug dissolution and oral absorption: physical and biopharmaceutical aspects. Pharmaceutical Research 1995; 11(12): 1561-72.
7. Pattewar S, Kasture S, Pande V and Sharma S: Self microemulsifying drug delivery system: a lipid based drug delivery system. Int J Pharm Sci Res 2016; 7(2): 443-52.
8. Suvarna V: Development and characterization of solid self-emulsifying drug delivery system containing nateglinide. Asian J Pharm 2017; 11: 27-36.
9. Mahmooda A and Bernkop-Schnurch AM: SEDDS: a game changing approach for the oral administration of hydrophilic macromolecular drugs. Adv Drug Del Rev 2019; 142: 91-101.
10. Hamdani J: Physical and thermal characterizations of Precirol1 and Compritol1 as lipophilic glycerides used for the preparation of controlled release matrix pellets. Int J Pharm 2003; 260: 4757.
11. Joshi Y, Kennedy JJ, Li P, Royce AE and Wagner RF: Microemulsion dosage forms of Valsartan and Methods of Making the Same. 2008 WO/2008/073731.
12. Khinchi MP and Gupta A: Self-emulsifying drug delivery system: a review. Asian Journal of Biochemical and Pharmaceutical Research 2011; 2(1): 359.
13. Huang Y, Zhang S, Shen H, Li J and Gao C: Controlled release of the nimodipine-loaded self-microemulsion osmotic pump capsules: Development and characteri-zation. AAPS Pharm Sci Tech 2018; 19: 1308-19.
14. Javed M, Mallikarjun C and Gan W: Enhancement of solubility and therapeutic potential of poorly soluble lovastatin by SMEDDS formulation adsorbed on directly compressed spray dried magnesium alumina metasilicate liquid loadable tablets: A study in diet induced hyper-lipidaemic rabbits. Asian J Pharm Sci 2015; 10: 40-56.
15. Malcolmson C, Satra C, Kantaria S, Sidhu A and Lawrence MJ: Effect of oil on the level of solubilization of testosterone propionate into non-ionic oil-in-water microemulsions. J Pharm Sci. 1998; 87: 109-16.
16. Mehta PP, Makanikar V and Parekh PP: Self emulsifying drug delivery system: a novel approach to enhance oral bioavailability of poorly soluble drugs. Journal of Pharmacy Research 2011; 4(7): 2191-94.
17. Mittal P, Rana AC, Bala R and Seth N: Lipid Based Self Micro Emulsifying Drug Delivery System (SMEDDS) For Lipophilic Drugs: An acquainted Review. International Research Journal of Pharmacy 2012; 2(12): 75-80.
18. Muranishi S: Absorption enhancers. Crit Rev Ther Drug Carrier System 1990; 7; 1-33.
19. Khadka P, Ro J, Kim H, Kim I, Tae J, Kim H, Min J, Yun G and Lee J: Science Direct 399 Pharmaceutical particle technologies: An approach to improve drug solubility, 400 dissolution and bioavailability. Asian J Pharm Sci 2014; 9: 304-16.
20. Patel AR and Vavia PR: Preparation and *in-vivo* evaluation of SMEDDS (Self Microemulsifying Drug Delivery System) containing fenofibrate. International Journal of Pharmacy 2005; 288: 27-34.
21. Patel PA, Chaulang GM, Akolkotkar A, Mutha SS, Hardikar S. and Bhosale AV: Self Emulsifying Drug Delivery System: A Review. Research J Pharm and Tech 2008; 1(4): 313-23.
22. Porter CJ and Chairman WN: *In-vitro* assessment of oral lipidbased formulations. Adv Drug Delivery Rev 2001; 50: S127-47.
23. Porter CJH and Chairman WN: Uptake of drugs into the intestinal lymphatics after oral administration. Adv Drug Delivery Rev 1997; 25: 71-89.
24. Rane SS and Anderson BD: What determines drug solubility in lipid vehicles: Is it predictable Adv Drug Deliv Rev 2008; 60: 638-56.
25. Sapra K and Sapra A: Self-emulsifying drug delivery system: A tool in solubility enhancement of poorly soluble drugs. Indo Global Journal of Pharmaceutical Science 2012; 2(3): 314.
26. Sunitha R, Satya SD and Aparna MVL: Novel self-emulsifying drug delivery system- an approach to enhance bioavailability of poorly water-soluble drugs. International J of Res in Pharmacy and Chemistry. 2011; 1(4): 828- 38.
27. Yi T, Wan J, Xu H and Yang X: A new solid self-micro emulsifying formulation prepared 396 by spray-drying to improve the oral bioavailability of poorly water soluble drugs, Eur J 397 Pharm Biopharm 2008; 70: 439-44.
28. Takada K and Murakami M: Glycyrrhizin preparations for transmucosal absorption. US Patent 6890547.
29. Tang J and Sun J: Self-emulsifying drug delivery system: strategy for improving oral delivery of poorly soluble drugs. Current Drug Therapy 2007; 2(1): 85-93.
30. Li XF, Liu XP and Rakesh K: Formulation and evaluation of etofibrate self-emulsifying drug delivery system (SEDDS). Eur J Pharm Med Res 2017; 4: 227-34.

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