



REVIEW ARTICLE

A review on self emulsifying drug delivery system: promising approach to enhance bioavailabilityDiksha Singh^{1*}, Sonam Ranga²¹Department of Pharmaceutics, Alwar Pharmacy College, MIA, Alwar affiliated to Rajasthan University of Health Sciences, Alwar, Rajasthan, India²Department of Pharmaceutics, Jaipur College of Pharmacy, Jaipur, affiliated to Rajasthan University of Health Sciences, Jaipur, Rajasthan, India

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ABSTRACT

Among the approaches to improve the oral bioavailability of the molecules, the use of self-emulsifying drug delivery system has been shown to be reasonably successful in improving the oral bioavailability of poorly water soluble and lipophilic drugs. SEDDS is a novel and versatile approach for overcoming the formulation difficulties with poor aqueous solubility and low bioavailability. SEDDS are the isotropic mixture of oils and surfactants even sometimes containing cosolvents, which emulsify to produce fine oil-in-water emulsions upon gentle agitation. These systems rapidly disperse in g.i.t yielding micro or nano emulsions containing the solubilised drug with droplet size 100-300 nm. For lipophilic drugs which have dissolution rate limited absorption, SEDDS may be promising strategy to improve rate and extent of oral absorption. This review article gives an overview of self emulsifying drug delivery system and also explains how SEDDS can improve the solubility and bioavailability of the poorly soluble drug.

Key words: Lipid based drug delivery system, self emulsifying drug delivery system, SEDDS, bioavailability.

INTRODUCTION:

Oral route is the easiest and most convenient route for non-invasive administration. It is the most cost-effective and leads the worldwide drug delivery market. Oral delivery of solid dosage form of lipophilic drug compounds is obstructed due to their hydrophobicity. Approximately 35-40% of new drug candidates have poor aqueous solubility. When a drug is administered by oral route the first step for it to get solubilised and then absorbed. The oral delivery of such drugs is frequently associated with low bioavailability, high inter and intra subject variability and lack of dose proportionality. Efforts are going on to enhance the oral bioavailability of lipophilic drugs in order to increase their clinical efficacy. To overcome these problems, new strategies were reported to increase solubility and bioavailability including complexation with cyclodextrins, solid dispersion (suspension), co precipitation, micronisation, salt formation, emulsion, use of micelles, and co grinding. In recent years, much attention has turned to lipid based formulations to improve oral bioavailability of poorly soluble drug candidates. The oral bioavailability is achieved by enhanced dissolution and solubilisation of the administered drug by stimulation of biliary and

pancreatic secretions, prolongation of gastric residence time, stimulation of lymphatic transport, and modulation of enterocytes-based drug transport and disposition. Emulsions are used as vehicles for the administration of drugs, especially due to its potential of enhancing the oral bioavailability of poorly absorbed drugs.

Self-emulsifying drug delivery systems (SEDDS) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. Their solubilising and absorption promoting effect is thought to lay in the reactivity of triglycerides and surfactants with the walls of the gastrointestinal tract. SEDDS formulations can be simple binary systems: lipophilic phase and drug, or lipophilic phase, surfactant and drug. The formation of a SEDDS requires the use of a co-surfactant to generate a micro emulsion. Recently, SEDDS have been formulated using medium chain tri-glyceride oils and non-ionic surfactants, the latter being less toxic. Upon per oral administration, these systems form fine emulsions (or micro-emulsions) in gastro-intestinal tract (GIT) with mild agitation provided by gastric mobility.

Self-emulsifying drug delivery systems (SEDDS) are mixtures of oils and surfactants, ideally isotropic, and sometimes containing cosolvents, which emulsify

spontaneously to produce fine oil-in-water emulsions when introduced into aqueous phase under gentle agitation. SEDDs can be administered orally in soft or hard gelatine capsules, which forms relatively stable oil-in-water emulsions upon aqueous dilution. Self emulsifying formulations spread readily in the gastrointestinal tract (GIT), and the GI motility of the stomach and the intestine provide the necessary agitation for self emulsification. These systems have the advantage that the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. SEDDS typically produces emulsion with a droplet size ranging between 100-300 nm. SEDDS are a promising approach for dosage form development of drugs with poor aqueous solubility and hence can be more useful for BCS Class II and IV drugs.^{1,2,3,4,5}

Purpose:

1. Highly important consideration in the formulation of SES (Self Emulsifying System) is effective incorporation of the drug, in terms of both the solubilization within the oil surfactant mix in order to allow a suitable solid dosage to form and once formed the effect that the drug may have on the emulsification properties.
2. The advantage of solid SES is in its dose reduction, if an improvement in oral bioavailability is established.^{4,5,6}

Challenges in Development of lipid based formulations:

One of the major hurdles in developing a lipid based formulation involves the selection of a suitable excipient. An ideal excipient should,

1. Be safe, inert and available at a purity level suitable for human use.
2. Not degrade during manufacturing or storage.
3. Be capable of solubilizing the drug dose in a volume not exceeding that of an oral capsule.
4. Preferably possess surface active properties to enable self-emulsification or complete dissolution of the drug dose.
5. Reliably and reproducibly enhance the oral bioavailability of the drug relative to a conventional formulation.
6. Be physically and chemically stable and compatible with a wide range of drugs and other excipients.
7. Be non hygroscopic and inert to the capsule shell or other packaging components.
8. Allow simple and efficient dosage form manufacture and permit ready scale-up from bench top to production-sized batches.^{5,6,7}

Advantages:

1. Protection of drug from GIT environment.
2. Selective targeting of drug toward specific absorption window in GIT.

3. Enhanced oral bioavailability.
4. Consistent drug absorption profile.
5. Better control of drug delivery profiles.
6. Versatility of dosage form as can be used with liquids or solids.
7. Predictable therapy due to reduced variability including food effects.
8. Drug payloads are high.
9. Protection of sensitive drug substances.

Need of Self-emulsifying drug delivery systems:

Oral delivery of poorly water-soluble compounds is to pre-dissolve the compound in a suitable solvent and fill the formulation into capsules. The oral drug delivery of hydrophobic drugs can be made possible by SEDDS. The main benefit of this approach is that pre-dissolving the compound over comes the initial rate limiting step of particulate dissolution in the aqueous environment within the GI tract. However, a potential problem is that the drug may precipitate out of solution when the formulation disperses in the GI tract, particularly if a hydrophilic solvent is used (e.g. polyethylene glycol). If the drug can be dissolved in a lipid vehicle there is less potential for precipitation on dilution in the GI tract, as partitioning kinetics will favour the drug remaining in the lipid droplets. Another strategy for poorly soluble drugs is to formulate a solid solution using a water-soluble polymer to aid solubility of the drug compound. For example, Poly Vinyl Pyrrolidone (PVP) and polyethylene glycol (PEG 6000) have been used for preparing solid solutions with poorly soluble drugs. One potential problem with this type of formulation is that the drug may favour a more thermodynamically stable state, which can result in the compound crystallizing in the polymer matrix. Therefore physical stability of such formulations needs to be assessed using techniques such as differential scanning calorimetric or X-ray crystallography. In this type of case SEDD system is a good option.^{8,9,10,5,6,7}

Disadvantages:

1. Traditional dissolution methods do not work, because these formulations potentially are dependent on digestion prior to release of the drug.
2. This in vitro model needs further development and validation before its strength can be evaluated.
3. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations needs to be developed and tested in vivo in a suitable animal model.

4. The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

Mechanism of self – emulsification:

The process by which self-emulsification takes place is not yet well understood. However, according to Reiss, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. In addition, the free energy of a conventional emulsion formation is a direct function of the energy required to create a new surface between the two phases and can be described by equation:

$$\Delta G = \Sigma N \pi r^2 \sigma$$

Where, G is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r, and s represents the interfacial energy.

With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area, and subsequently, the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents, which form a monolayer around the emulsion droplets, and hence, reduce the interfacial energy, as well as providing a barrier to coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative (then, the emulsification process occurs spontaneously).

Emulsification requiring very little input energy involves destabilization through contraction of local interfacial regions. For emulsification to occur, it is necessary for the interfacial structure to have no resistance to surface shearing. In earlier work, it was suggested that the ease of emulsification could be associated with the ease by which water penetrates into the various LC or gel phases formed on the surface of the droplet. The addition of a binary mixture (oil/non-ionic surfactant) to water results in interface formation between the oil and aqueous-continuous phases, followed by the solubilization of water within the oil phase owing to aqueous penetration through the interface. This will occur until the solubilization limit is reached close to the interface. Further aqueous penetration will result in the formation of the dispersed LC phase. As the aqueous penetration proceeds, eventually all material close to the interface will be LC, the actual amount depending on the surfactant concentration in the binary mixture. Once formed, rapid penetration of water into the aqueous cores, aided by the gentle agitation of the self-emulsification process, causes interface disruption and droplet formation. The high

stability of these self-emulsified systems to coalescence is considered to be due to the LC interface surrounding the oil droplets. The dielectric studies provided evidence that the formation of the emulsions may be associated with LC formation, although the relationship was clearly complex. The above technique also pointed out that the presence of the drug may alter the emulsion characteristics, possibly by interacting with the LC phase. However, the correlation between the spontaneous emulsification and LC formation is still not definitely established.^{11, 12, 8,9,10}

Construction of phase diagram:

The relationship between the phase behaviour of a mixture and its composition can be captured with the aid of a phase diagram. Compositional variables can also be studied as a function of temperature and, pressure, although with the exception of microemulsions prepared using supercritical or near critical solvents, or with liquefied chlorofluorocarbon and HFA propellants, the large majority of systems are studied under conditions of ambient pressure. The phase behaviour of simple microemulsion systems comprising oil, water and surfactant can be studied with the aid of ternary phase diagram in which each corner of the diagram represents 100% of that particular component. The Co-surfactant is also amphiphilic with an affinity for both the oil and aqueous phases and partitions to an appreciable extent into the surfactant interfacial monolayer present at the oil-water interface. The Co-surfactant need not necessarily be capable of forming association structures in its own right. A wide variety of molecules can function also surfactants including non-ionic surfactants, alcohols, alkanolic acids, alkanediols and alkyl amines. Surprisingly few studies have examined the effect of drug on phase behavior, this is despite the fact that large numbers of drug molecules are themselves surface active and as such would be expected to influence phase behaviour. In the case where four or more components are investigated, pseudo-ternary phase diagrams are used where a corner will typically represent a binary mixture of two components such as surfactant / Co-surfactant, water /drug or oil / drug. The number of different phases present for a particular mixture can be visually assessed. Constructing phase diagrams is time consuming, particularly when the aim is to accurately delineate a phase boundary, as the time taken for the system to equilibrate can be greatly increased as the phase boundary is approached. Heat and sonication are often used, particularly with systems containing nonionic surfactants, to speed up the process. Care must be taken to ensure not only that the temperature is precisely and

accurately controlled, but also that observations are not made on metastable system. Clearly, however, time constraints impose a physical limit on the length of time system can be left to equilibrate and consequently the elimination of metastable states can be difficult to ensure in practice, although centrifugation can be useful to speed up any separation. Within this region, and indeed other multi phase regions of the ternary phase diagram, microemulsions can exist in equilibrium with excess water or oil phases. Microemulsions stabilized by non-ionic surfactants, especially those based on polyoxyethylene, are very susceptible to temperature because a decrease in surfactant solubility occurs with increasing temperature, and as a result systems stabilized by non-ionic surfactants or mixtures thereof often have characteristic phase inversion temperatures (PITs), with the PIT of the microemulsion varying with a range of experimental factors including the amount and nature of

the oil present and the nature of the surfactant(s) present. Ternary phase diagrams were constructed using Capmul PG8 (propylene glycol monocaprylate) as the oil, Tween 20 (polysorbate 20) and/or Cremophor EL (polyoxyl 35 castor oil) as surfactants.

A titration method is employed to construct phase diagram. Mixture of oil with surfactant is prepared at different ratios (e.g. 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10) into different vials. A small amount of water in 5 % (w/w) increment is added into the vials. Following each water addition the mixture in vials is centrifuged for 2 to 3 minute and is incubated at 25°C for 48 hrs with gentle shaking. The resulting mixture is evaluated by visual and microscopic observation. For phase diagram the micro emulsion is the region of clean and isotropic solution. Coarse emulsion is the region of cloudy dispersion.^{13, 14,8,9,10,11}

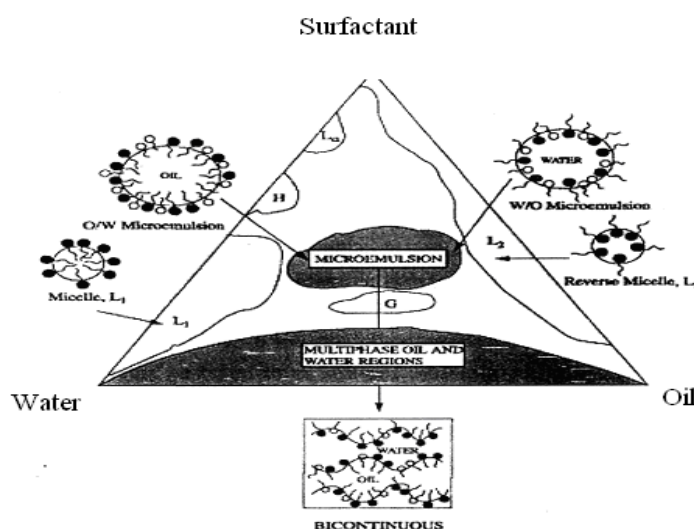


Figure 1: Example of pseudo ternary phase diagram.

Composition of Self-emulsifying drug delivery systems

The self-emulsifying process is depends on

1. The nature of the oil–surfactant pair
2. The surfactant concentration
3. The temperature at which self-emulsification occurs.

Oil:

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. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDS. Modified or hydrolyzed vegetable oils

have contributed widely to the success of SEDDS owing to their formulation and physiological advantages. Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.

Surfactant:

Non-ionic surfactants with high hydrophilic– lipophilic balance (HLB) values are used in formulation of SEDDS (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30–60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous

media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.

Co-solvent:

Co-solvents like diethylene glycol monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the co surfactant in the microemulsion systems.^{14, 15, 4,6,7,8,9,10}

Table: 1 Example of lipid ingredients, surfactant, co-surfactants and co-solvents used in formulations

Lipid Ingredient	Surfactants	Co-surfactants/co-solvents
Corn oil, Olive oil, Oleic oil, Sesame oil, Hydrogenated Soyabean oil, Hydrogenated Vegetable oils, Peanut oil, Beeswax, Medium chain mono-and di-glycerides, Fractioned triglyceride of palm seed oil, Mixture of mono- and di-glycerides of caprylic/capric acid, Fractionated triglyceride of coconut oil, DL-alpha-Tocopherol.	Polysorbate 20 (Tween 20), Polysorbate 80 (Tween 80), Sorbitan monooleate (Span 80), Polyoxy-40- hydrogenated castor oil (Cremophor RH40), Polyoxyethylated glycerides (Labrafil M 2125 Cs), Polyoxyethylated oleic glycerides (Labrafil M1944 Cs), Labrasol	Ethanol, Glycerin, Polypylene glycol, Polyethylene glycol, Transcutol.

Formulation of Self-emulsifying drug delivery systems:

With a large variety of liquid or waxy excipients available, ranging from oils through biological lipids, hydrophobic and hydrophilic surfactants, to water soluble cosolvents, there are many different

Combinations that could be formulated for encapsulation in hard or soft gelatin or mixtures which disperse to give fine colloidal emulsions. The following should be considered in the formulation of a SEDDS:

1. The solubility of the drug in different oil, surfactants and cosolvents.
2. The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram.
3. The preparation of SEDDS formulation by dissolving the drug in a mixture of oil, surfactant and co-solvent.

The addition of a drug to a SEDDS is critical because the drug interferes with the self-emulsification process to a certain extent, which leads to a change in the optimal oil-surfactant ratio. So, the design of an optimal SEDDS

requires preformulation-solubility and phase-diagram studies. In the case of prolonged SEDDS, formulation is made by adding the polymer or gelling agent. The level of active moiety is kept constant according to the required dose.^{15, 16,10,11,14}

EVALUATION OF SEDDS:

Thermodynamic stability studies:

The physical stability of a lipid –based formulation is very important for its performance as it can be adversely affected by precipitation of the drug in excipient matrix. Poor physical stability of formulation can lead to phase separation of excipients which affects bioavailability as well as therapeutic efficacy. Also the incompatibilities between formulation and the gelatin capsules shell can lead to brittleness or deformation, delayed disintegration, or incomplete release of drug. The following cycles are carried out for these studies-

- 1) Heating cooling cycle:** Six cycles between refrigerator temperature (4°C) and elevated temperature (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: formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. Those formulations that does not show any phase separation are taken for the freeze thaw stress test.

3) Freeze thaw cycle: Three freeze thaw cycles b/w -21°C and 25°C with storage at each temperature for not less than 48 hours. Those formulations passed this test show good stability with no phase separation, creaming, or cracking.

4) Dispersibility test: The efficiency of self-emulsification of oral nano or micro emulsion is assessed using a standard USP XXII dissolution apparatus 2. One ml of each formulation was added to 500 mL of water at 37 ± 0.5 OC. 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:

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

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

3. Grade C: Fine milky emulsion that formed within 2 min.

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

5) 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 nanoemulsion when dispersed in GIT. While formulation falling in Grade C could be recommend for SEDDS formulation.

6) Turbidimetric Evaluation: Turbidity is a parameter for determination of droplet size and self emulsification time. Nepheloturbidimetric evaluation is done to monitor the growth of emulsification. Fixed quantity of SEDDS is added to fixed quantity of suitable medium (0.1N hydrochloric acid or Phosphate Buffer) under continuous stirring (50 rpm) on 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).

7) Viscosity Determination: The SEDDS system is generally administered in soft gelatin or hard gelatine capsules. So, it can be easily pourable into capsules and such system should not too thick to create a problem. The rheological properties of the micro emulsion are

evaluated by Brookfield viscometer. This viscosities determination conform whether the system is w/o or o/w. If system has low viscosity then it is o/w type of the system and if high viscosity then it is w/o type of the system.

8) Droplet Size Analysis And Particle Size Measurements : The droplet size of the emulsions is determined by photon correlation spectroscopy (which analyses the fluctuations in light scattering due to Brownian motion of the particles) using a Zetasizer 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.

9) Robustness to dilution: Emulsions upon dilution with various dissolution media should not show any phase separation or precipitation of drug even after 12hrs of storage, that formulation is considered as robust to dilution.

10) Self Emulsification Time: The self emulsification time is determined by using USP dissolution apparatus II at 50 r/ min, where 0.5 g of SEDDS formulation is introduced into 250 ml of 0.1 N HCL or 0.5% SLS solution. The time for emulsification at room temperature is indicated as self emulsification time for the formulation.

11) In- vitro Dissolution Testing : The quantitative *in-vitro* dissolution studies are carried out to assess drug release from oil phase into aqueous phase by USP type II dissolution apparatus using 500 ml of simulated gastric fluid containing 0.5% w/v of SLS at 50 r/ min and maintaining the temperature at 37 ± 0.5 °C. Aliquots of samples are withdrawn at regular intervals of time and volume withdrawn is replaced with fresh medium. Samples taken are then analyzed by using UV spectrophotometer or any other suitable technique

12) Drug Content: Drug from pre-weighed SEDDS is extracted by dissolving in suitable solvent. Drug content in the solvent extract was analyzed by suitable analytical method against the standard solvent solution of drug.^{16, 15,3,4,6,8,9,10,11}

TECHNIQUES OF SOLID SELF EMULSIFYING DRUG DELIVERY SYSTEM DEVELOPMENT:

Techniques are chosen on the basis of properties of lipid excipient. The techniques reviewed here under facilitate the transformation of liquid or semi-solid formulations into solid particles (powders, granules or pellets) which could subsequently be filled into capsules, sachets or compressed into tablets.

1) Spray Cooling: The molten droplets are sprayed into cooling chamber, which will congeal and re-crystallize into spherical solid particles that fall to the bottom of the chamber and subsequently collected as fine powder. The fine powder may then be used for development of solid dosage forms tablets or direct filling into hard shell capsules. Many types of equipment are available to atomize the liquid mixture and to generate droplets: rotary, pressure, two-fluid or ultrasonic atomizers.

2) Spray Drying: Spray drying is defined as a process by which a liquid solution is sprayed into a hot air chamber to evaporate the volatile fraction. Polyoxylglycerides (lauroyl or stearyl) have been used alone or in combination with a solid carrier (silicon dioxide) to form microparticles of etoricoxib and glibendamide. Dry emulsion technology solves the stability problems associated with classic emulsions (phase separation, contamination by micro-organism, etc.) during storage and helps also avoid using harmful or toxic organic solvents. Dry emulsions may be redispersed into water before use. Medium chain triglycerides are commonly used as oil phase for these emulsions.

3) Adsorption on Solid Carriers: Solid carriers are used for the adsorption of liquid formulation to get final solid product and it will be free flowing so that it can be compressed or directly filled in hard gelatine capsules. A significant benefit of the adsorption technique is good content uniformity as well as the possibility for high lipid exposure. The adsorption technique has been successfully applied to gentamicin and erythropoietin with caprylocaproylpolyoxylglycerides (Labrasol) formulations that maintained their bioavailability enhancing effect after adsorption on carriers.

4) Melt Granulation: Melt granulation or pelletization is a one step process allowing the transformation of a powder mix containing the drug into granules or spheronized pellets. The melted binder forms liquid bridges with the powder particles that shape into small agglomerates (granules) which can, by further mixing under controlled conditions transform to spheronized pellets. The main parameters that control the granulation process are impeller speed, mixing time, binder particle size, and the viscosity of the binder during melt granulation. Nucleation (onset of granule formation) is largely affected by binder viscosity at high impeller speed and binder particle size at low speed. Depending on the combination of process parameters, two distinct mechanisms namely "distribution" and "immersion" may be at play in the development of granules. Fine or atomized excipients with low viscosity at high impeller speed favour a homogenous "distribution" of the binder

onto the surface of the powder. Immersion of the powder on the other hand is the preferred mechanism which is assisted by combination of large binder particles possessing high viscosity and mixing under low impeller speed. The granule size distribution is controlled by the combined effect of the impeller and chopper speeds. Generally, lipids with low HLB and high melting point are suitable for sustained release applications. Semisolid excipients with high HLB on the other hand may serve in immediate release and bioavailability enhancement. The progressive melting of the binder allows the control of the process and the selection of the granule's size. Also, the melt granulation process may be used for adsorbing semi-solid self emulsifying systems on solid neutral carriers (mainly silica and magnesium alumina metasilicate). The main advantages of melt granulation/pelletization with lipids are process simplicity (one-step), absence of solvents, and more importantly the potential for the highest drug loading capacity –85% theoretically, and up to 66% actually reported in the literature.

5) Melt Extrusion/ Spheronisation: Extrusion is a process of converting a raw material with plastic properties into a product of uniform shape and density by forcing it through a die under controlled temperature, product flow and pressure conditions. This approach has been successfully tried for 17 β - estradiol and two model drugs with surfactants such as sucrose monopalmitate, lauroylpolyoxyl glycerides and polysorbate 80 (Tween[®] 80). Gelucire 44/14 to be used directly in the core of the formulation matrix. An innovative "system in cylinder" moulding technique was recently employed to develop a dual purpose (enhanced bioavailability and controlled release) formulation with propranolol hydrochloride. Melt extrusion is a solvent free process that allows high drug loading as well as content uniformity for low dose high potency actives.

6) Supercritical Fluid Based Method: Lipids may be used in supercritical fluid based methods either for coating of drug particles, or for producing solid dispersions. For environmental reasons, the preferred supercritical fluid of choice is supercritical carbon dioxide. Examples include controlled release applications using glyceryl trimyristate (Dynasan[™] 114) and stearylpolyoxylglycerides (Gelucire[®] 50/02).

7) Solid Lipid Nanoparticles and Nanostructured Lipid Carriers: SLN and NLC are two types of submicronsize particles (50– 1000 nm) composed of physiologically tolerated lipid components. SLN are produced by high-pressure homogenization of the solid matrix and drug with an aqueous solution of the glyceryldibehenate as

solid lipid matrix and poloxamers 188 or polysorbates 80 as surfactants. They typically contain a liquid lipid excipient such as medium chain triglycerides in addition to classic components of SLN. They have been mainly used for controlled-release applications in oral, intravenous or topical route.^{16, 4, 3, 4, 7, 8, 9}

DOSAGE FORM OF SELF EMULSIFYING SYSTEM:

1. Self-emulsifying capsule: It is a capsule containing liquid or semisolid form of SES. In the GIT, the capsules get dispersed to SES uniformly in the fluid to micron size, enhancing the bioavailability. Second type of self-emulsifying capsule is solid SES filled into capsule.

2. Self-emulsifying sustained/controlled release tablets: The preparation of self emulsifying tablets depends on combination of lipids and surfactants. Researchers are evaluated some parameters before formulating self emulsifying tablets, they are colloidal silicates X1, magnesium stearate mixing time X2, and compression force X3, on hardness and coenzyme Q10 (CoQ10) dissolution from tablets of eutectic-based SMEDDS. The optimized conditions (X1 = 1.06%, X2 = 2 min, X3 = 1670 kg) were achieved by a face centered cubic design. The amount of solidifying excipients reduced for transformation of SEDDS into solid dosage forms, a gelled SEDDS has been developed by Patil et al. In their study, colloidal silicon dioxide (Aerosil 200) was selected as a gelling agent for the oil-based systems, which served the dual purpose of reducing the amount of required solidifying excipients and aiding in slowing down of the drug release.

3. Self emulsifying suppositories: Some investigators proved that solid-SEDDs could not only increase the GI absorption but also increase the rectal/vaginal adsorption. Glycyrrhizin, hardly achieves therapeutic plasma concentrations by oral route, but can achieve acceptable therapeutic levels for chronic hepatic diseases by either vaginal or rectal SE suppositories. The formulation included glycyrrhizin and a mixture of a C6–C18 fatty acid glycerol ester and a C6–C18 fatty acid macrogol ester.

4. Self-emulsifying sustained/controlled release pellets: Self – emulsifying sustained / controlled release pellets can be prepare by incorporating drugs into SES, thereby improved their rate of release, and then by coating pellets with a water-insoluble polymer that reduces the rate of drug release. To formulate and prepare SEDDS, there were some basic guidelines are considered: safety, compatibility, drug solubility, efficient self emulsification efficiency and droplet size, etc. Pellets are multiple unit dosage forms, they may provide many advantages than conventional solid dosage forms, due to some factors like

flexibility of manufacture, reducing intra subject and inter subject variability of plasma profiles and minimizing GI irritation without lowering drug bioavailability. Thus, it is very interesting to combine the advantages of pellets with those of SEDDS by SE pellets. They were prepared by extrusion/Spheronisation and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained monodiglycerides and Polysorbate 80.

5. Self-emulsifying nanoparticles : For the production of self emulsifying nanopartides, nanoparticle technology might be used successfully. Under these one of the techniques called solvent injection is used. In this technique, molten lipid mass was prepared, which contains the mixture of lipid, surfactant, and drug. And then this lipid mass transferred into a non-solvent in a drop wise manner and mix them. And thereafter filter them and dried. By this method we get the nanoparticles (about 100nm) with a drug loading efficiency of 74%39. More recently, a novel nanopartide drug delivery system consisting of chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel (PTX) has been developed. The SE property of GMO enhanced the solubility of PTX and provided a basis for chitosan aggregation, in the meantime causing near 100% loading and entrapment efficiencies of PTX. And one more study was to prepare a self nanoemulsifying system (SNES) containing model lipophilic drug, felodipine (FLD), to improve its solubility. The SNES was formulated using altering amounts of Miglyol 840 (as an oil), Cremophor EL (as a surfactant), and Capmul MCM (as a co-surfactant).

6. Self-emulsifying beads: Self-emulsifying beads can be formulated as a solid dosage form by using less solidifying excipient. Patil et al discovered that deposition of SES into micro porous polystyrene beads was done by solvent evaporation. Porous polystyrene beads (PPB) with complex internal void structures were typically produced by copolymerizing styrene and divinyl benzene. It is inert and stable over a wide range of pH, temperature and humidity. Geometrical features such as bead size and pore architecture of PPB, were found to preside over the loading efficiency and *in vitro* drug release from SES loaded PPB.

7. Self emulsifying solid dispersions: Solid dispersions could increase the dissolution rate and bioavailability of poorly water soluble drugs. But some manufacturing difficulties and stability problems are arised ,to overcome these problems self emulsifying excipients like Gelucire1 44/14, Gelucire1 50/02, Labrasol1, Transcutol and TPGS (tocopheryl polyethylene glycol 1000 succinate) have been widely used. Gupta et al. prepared SE solid dispersion granules using the hot-melt granulation

method. Seven drugs, including four carboxylic acid containing drugs, a hydroxyl containing drug, an amide-containing drug (phenacetin) and a drug with no proton donating groups (progesterone) were chosen. Gelucire150/13 was used as the dispersion carrier; where as Neusilin US2 was used as the surface adsorbent.

8. Self-emulsifying sustained release microspheres: Zedoary turmeric oil (ZTO; a traditional Chinese medicine) shows effective pharmacological actions like tumor suppressive, antibacterial, and antithrombotic activity. Solid SE sustained release microspheres using the quasiemulsion- Solvent diffusion method of the spherical crystallization technique, in this technique ZTO used as oil phase. ZTO release activities might be controlled by the ratio of hydroxyl propyl methylcellulose acetate succinate to Aerosil 200 in the formulation. After oral administration of such microspheres to rabbits, the plasma concentrations were achieved with increased bioavailability of 135.6% with respect to the conventional liquid SEDDS.

9. Self-emulsifying implants: Self-emulsifying implants have very much improved efficacy under application of SSEDDS, since they have short half life. As an example, 1, 3- bis (2 chloroethyl)-1-nitrosourea (carmustine, BCNU) is a chemotherapeutic agent used to treat malignant brain tumors. In order to enhance its stability compared with that released from poly (d,l-lactide-coglycolide)(PLGA) wafer implants, SES was formulated with tributyrin, Cremophor RH 40 (polyoxyl40 hydrogenated castor oil) and Labrafil 1944 (polyglycolized glyceride). Therefore SES increased in vitro half-life of BCNU up to 130 min compared with 45 min of intact BCNU. *In-vitro* release of BCNU from SE PLGA wafers were extended up to 7days. Such wafers had higher in vitro antitumor activity and were less prone to hydrolysis than those wafers without of SES.^{18, 19, 20, 7, 8, 9}

BIOPHARMACEUTICAL ASPECTS:

The ability of lipids and/or food to enhance the bioavailability of poorly water-soluble drugs has been comprehensively reviewed. Although incompletely understood, the currently accepted view is that lipids may enhance bioavailability *via* a number of potential mechanisms, including:

1. Alterations (reduction) in gastric transit: thereby slowing delivery to the absorption site and increasing the time available for dissolution.

2. 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

3. 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.

4. 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 glycoprotein efflux pump, and may also reduce the extent of enterocyte-based metabolism.

5. 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.

6. Effect of oils on the absorption: Such formulations form a fine oil-in-water emulsion with gentle agitation, which may be provided by gastrointestinal motility. 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 hydrophobic compound.^{21,18,19,20}

FACTORS WHICH AFFECT SEDDS:

1. Polarity of the Lipophilic Phase:

The polarity of the lipid phase is one of the main factors that govern the drug release from the micro-emulsions. The polarity of the droplet is governed by the HLB, the chain length and degree of unsaturation of the fatty acid, the molecular weight of the hydrophilic portion and the concentration of the emulsifier. In fact, the polarity reflects the affinity of the drug for oil and/or water, and the type of forces formed. The high polarity will promote a rapid rate of release of the drug into the aqueous phase. This is confirmed by the observations of Sang-Cheol Chi, who observed that the rate of release of idebenone from SEDDS is dependant upon the polarity of

the oil phase used. The highest release was obtained with the formulation that had oil phase with highest polarity.

2. Nature and Dose of the Drug:

Drugs which are administered at very high dose are not suitable for SEDDS unless they have extremely good solubility in at least one of the components of SEDDS, preferably lipophilic phase. The drugs which have limited or less solubility in water and lipids are most difficult to deliver by SEDDS. The ability of SEDDS to maintain the drug in solubilised form is greatly influenced by the solubility of the drug in oil phase. If surfactant or co-surfactant is contributing to the greater extent in drug solubilisation then there could be a risk of precipitation, as dilution of SEDDS will lead to lowering of solvent capacity of the surfactant or co-surfactant. Equilibrium solubility measurements can be carried out to anticipate potential cases of precipitation in the gut. However, crystallisation could be slow in the solubilising and colloidal stabilizing environment of the gut. Pouton's study reveal that such formulations can take up to five days to reach equilibrium and that the drug can remain in a super-saturated state for up to 24 hours after the initial emulsification event. It could thus be argued that such products are not likely to cause precipitation of the drug in the gut before the drug is absorbed, and indeed that super-saturation could actually enhance absorption by increasing the thermodynamic activity of the drug. There is a clear need for practical methods to predict the fate of drugs after the dispersion of lipid systems in the gastrointestinal tract.^{21, 17, 18, 20}

APPLICATIONS:

1. Enhancement in Solubility and Bioavailability:

Improvement in solubility observed if a drug is loaded in SEDDS because it circumvents the solubilization or dissolution step in case of class-2 drugs (low solubility/high permeability). A moderately hydrophobic drug ketoprofen (Non-steroidal anti-inflammatory drug), is a drug of choice for sustain release formulation has a side effect of gastric irritation during chronic therapy. Ketoprofen shows incomplete release from sustain release formulation due to its low solubility. Complete release of ketoprofen from sustains release formulation by loaded it in nano crystalline form. Various formulation approaches have been used to achieve sustain release, improvement in bioavailability, and decrease in side effect of gastric irritation of ketoprofen include preparation of matrix pellets of nano-crystalline ketoprofen, sustained release ketoprofen microparticles and formulations, floating oral ketoprofen systems, and transdermal systems of ketoprofen. Different problems

like processing, stability and economic problem arises during preparation and stabilization of nanocrystalline or improved solubility forms of drug so by loading drug in SEDDS such problems can be overcome. SEDDS formulation enhances the bioavailability by increasing solubility of drug and also decreases the gastric irritation. Also incorporation of gelling agent in SEDDS sustains the release of ketoprofen. In SEDDS, by the interaction b/w lipid matrix and water a fine particulate oil-in-water emulsion will form and this emulsion droplet will deliver the drug in dissolved form to the gastro intestinal mucosa readily accessible for absorption. Therefore, increase in AUC i.e. bioavailability and C_{max} is observed with many drugs when presented in SEDDS.^{22, 20, 21}

2. Super saturable S-SMEDDS:

S-SMEDDS have been developed to overcome the toxic effect of surfactant or GI side effects produced by surfactant when used in very high concentration as typically used in SMEDDS. When the formulation is released from an appropriate dosage form into an aqueous medium, S-SMEDDS forms a protected supersaturated solution of drug and this supersaturation is intended to enhance the thermodynamic activity to the drug in spite of its solubility limit, therefore enhancement in driving force for transit into and across the biological membrane will be obtained. Reduced level of surfactant and a polymeric precipitation inhibitor (HPMC and related cellulose polymers) to yield and stabilize a drug in a temporarily supersaturated state are contents of S-SMEDDS formulation. S-SMEDDS of paclitaxel in which HPMC used as precipitation inhibitor was developed. Formation of a microemulsion, followed by slow crystallization of paclitaxel on standing occur in *in-vitro* dilution study of S-SMEDDS formulation. This result indicated that the system was supersaturated with respect to crystalline paclitaxel, and the supersaturated state was prolonged by HPMC in the formulation. In the absence of HPMC, the SMEDDS formulation underwent rapid precipitation, yielding a low paclitaxel solution concentration. A pharmacokinetic study showed that the paclitaxel S-SMEDDS formulation produced approximately a 10-fold higher maximum concentration (C_{max}) and a 5-fold higher oral bioavailability (F ~ 9.5%) compared with that of the orally administered Taxol formulation (F ~ 2.0%) and the SMEDDS formulation without HPMC (F ~ 1%). Reduced quantity of surfactant can be used with HPMC in order to produce a temporarily supersaturated state with reduced solubilisation by applying this approach.

Thus a high free drug concentration would be obtained through generating and maintaining a supersaturated

state *in-vivo* and to increase the driving force for absorption. Better toxicity/safety profile than the conventional SMEDDS formulation will be obtained by using this approach as S-SMEDDS contain reduced amount of surfactant. However, the underlying mechanism of the inhibited crystal growth and stabilized supersaturation by means of these polymers is poorly understood.

3. Solid Self-emulsifying drug delivery systems:

SMEDDS are normally prepared as liquid dosage forms that can be administered in soft or hard gelatin capsules, which have some disadvantages especially in manufacturing process for soft and leakage problem with hard gelatin capsules. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form (tablets, capsules). A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/Spheronisation to provide a good *in-vitro* drug release (100% within 30 min, T50% at 13 min). The same dose of progesterone (16 mg) in pellets and in the SEDDS liquid formulation resulted in similar AUC, Cmax and Tmax values. A method of producing self-emulsifying pellets by wet granulation of a powder mixture composed of microcrystalline cellulose, lactose and nimesulide as model drug with a mixture containing mono- and diglycerides, polysorbate 80 and water has been investigated. The pellets produced with oil to surfactant ratio of 1:4 (w/w) showed improved performance in permeation experiments.

4. Protection from Biodegradation:

Drugs for which both solubility and degradation is low in the GI tract contribute to a low oral bioavailability, SMEDDS is useful for such drugs due to ability to reduce

degradation as well as improve absorption. Drugs which undergo degradation in physiological system due to some reasons like acidic PH in stomach, enzymatic degradation or hydrolytic degradation can be protected from these degradation processes by loading them in SMEDDS, as liquid crystalline phase in SMEDDS act as a barrier between degrading environment and the drug. Acetylsalicylic acid (log P = 1.2, Mw=180) is a drug readily hydrolyzed to salicylic acid in an acid environment and because of this it degrades in GI tract. When this drug is loaded in SMEDDS formulation and compare with commercial formulation, good plasma profile will be observed with SMEDDS formulation as compare to reference formulation. Bioavailability enhancement (73%) also occurs when SMEDDS formulation used. This suggests that the SMEDDS formulation has a capacity to protect drugs from degradation in the GI tract.

5. Sustain Release from SMEDDS:

Due to the wide range of structures occurring in them, SMEDDS display a rich behaviour regarding the release of solubilised material. Thus in case of O/W microemulsion, hydrophobic drugs solubilised mainly in the oil droplets, experience hindered diffusion and are therefore released rather slowly (depending on the oil/water partitioning of the substance). Water soluble drugs, on the other hand, diffuse essentially without obstruction (depending on the volume fraction of the dispersed phase) and are release fast. For balanced microemulsion, relatively fast diffusion and release occur for both water soluble and oil soluble drugs due to the bicontinuous nature of microemulsion "structure". Apart from the microemulsion structure, the microemulsion composition is important for the drug release rate.

Table 2: marketed seeds formulations²³

Brand name	Drug used	Dosage form	Company
Neural	Cyclosporine	SGC	Novartis
Norvir	Ritonavir	SGC	Abott laboratories
Fortovase	Saquinavir	SGC	Hoffmann roche
Agenerase	Amprenavir	SGC	GSK
Convulex	Valporic acid	SGC	Pharmacia

CONCLUSION:

SEDDS will be a promising approach in lipid based formulations for improving the oral bioavailability of poorly soluble drugs. Since development of this technique will enhance the use of novel application in drug delivery system. Despite of certain challenges there is great prospect in the use of lipid formulation. Care has

to be taken while preparing the dosage form of the formulation as small interference may interrupt the stability of the formulation. Hence the drug should be stable with its component or else the chances of precipitation of the drug may take place. Self emulsifying drug delivery system can be formulated in solid or liquid forms also.

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