Indo Global Journal of Pharmaceutical Sciences, 2012; 2(3): 313-332

INDO GLOBAL JOURNAL OF PHARMACEUTICAL SCIENCES
ISSN 2249- 1023

Self Emulsifying Drug Delivery System: A Tool in Solubility Enhancement of Poorly Soluble Drugs

Kavita Sapra[a*], Ashu Sapra[b], S K Singh[a], Saloni Kakkar[b]

[a] *Department of Pharmaceutical Sciences, G J University of Science & Tech., Hisar(Haryana), India*

[b] *Department of Pharmaceutical Sciences,M D University, Rohtak(Haryana), India*

Address for Correspondance: ashumdurohtak@gmail.com

ABSTRACT: Low aqueous solubility and thereby low oral bioavailability is a major concern for formulation scientist as many recent drugs are lipophillic in nature and their lower solubility and dissolution is a major drawback for their successful formulation into oral dosage forms. Aqueous solubility of drugs can be increased by different methods such as salt formation, solid dispersion, complex formation but Self Emulsifying Drug Delivery System (SEDDS) is gaining more attention for improving the solubility of lipophillic drugs. SEDDS are ideally isotropic mixtures of drug, oil, surfactant and/or co surfactant. They spontaneously form emulsion on mixing with water with little or no energy input. Generally SEDDS are prepared using triglycerides and non ionic surfactants. The present review provides an updated account of the advancements in SEDDS with regard to the selection of lipid systems for current formulations, dosage forms for SEDDS, solidification techniques, characterization and their applications.

KEYWORDS: Aqueous Solubility; Self Emulsifying Drug Delivery System; Surfactant; Co Surfactant; Emulsification Efficiency.

INTRODUCTION

The oral route is the most preferred route of drug delivery for treatment of a number of diseases. Nearly 35 to 40% of newly launched drugs possess low aqueous solubility which leads to their poor dissolution and thereby low bioavailability, resulting in high intra & inter subject variability & lack of dose proportionality. For these drugs absorption rate from gastrointestinal tract is mainly governed by dissolution and improvement in solubility may lead to enhanced bioavailability. [1]

There are number of techniques to overcome such problems arising out of low solubility and bioavailability, which may result into improved therapeutic efficacy of these drugs. The techniques like complex formation with cyclodextrins, solid dispersion, liposome formation, co precipitation, micronization, salt formation, use of micelles, co grinding and emulsification had been used for improving the dissolution profile of drugs with low solubility. [2-5]

Recently a new technique, Self Emulsifying Drug Delivery System (SEEDS) has been developed to enhance the solubility of drug. SEDDS are defined as isotropic mixtures of natural or synthetic oils, solid or liquid surfactants or alternatively, one or more hydrophilic solvents & co-solvents/co-surfactants. [1]

Properties of SEDDS

- They are able to self emulsify rapidly in gastro-intestinal fluids & under the influence of gentle agitation provided by Peristaltic and other movements of gastro intestinal tract, they form a fine o/w emulsion. [1,6]
- They can effectively incorporate drug (hydrophobic or hydrophilic) within the oil surfactant mixture.
- They can be used for liquid as well as solid dosage forms.
- They require lower dose of drug with respect to conventional dosage forms.

Advantages associated with SEDDS

- Protection of drug from GIT environment. [6]
- Selective targeting of drug toward specific absorption window in GIT. [6]
- Enhanced oral bioavailability. [7]
- Consistent drug absorption profile.
- Better control of drug delivery profiles.
- Versatility of dosage form as can be used with liquids or solids.
- Predictable therapy due to reduced variability including food effects. [8]
- Drug payloads are high.
- Protection of sensitive drug substances.

Mechanism of self Emulsification

Self emulsifying processes are related to the free energy, ΔG [9] given by:

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

Where, N = Number of droplets with radius r

σ = Interfacial energy

It is apparent from the above equation that spontaneous formation of interface between oil & water phase is not favorable due to higher energy level. The system commonly classified as SEDDS have not yet been shown to emulsify spontaneously in true thermodynamic sense.

Groves & Mustafa developed a method of quantitatively assessing the ease of emulsification by monitoring the turbidity of oil-surfactant system in aqueous system, using phosphate nonylphenoxylate (PNE) and phosphate fatty alcohol ethoxylate (PFE) in n-hexane and suggested that emulsification process may be associated with the ease with which water penetrates the oil-water interface, with formation of liquid crystalline phase resulting in swelling at interface, thereby resulting in greater ease of emulsification. [10]

Pouton has said that the emulsification capacities of surfactant may be related to phase inversion behavior of the system. If one increases the temperature of the oil in water system which is stabilized by using non-ionic surfactants, the cloud point of the surfactant will be reached followed by phase inversion. [11]

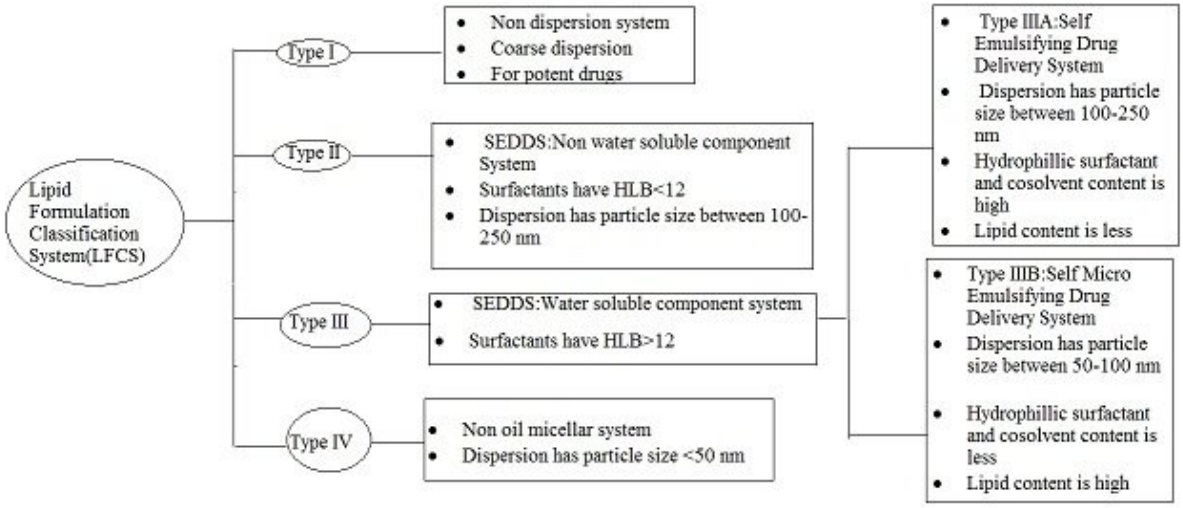
The surfactant is highly mobile at phase inversion temperature due to which o/w interfacial energy is minimized leading to a reduction in energy required for emulsification.

Pouton has suggested that the specificity of surfactant combination required to allow spontaneous emulsification is associated with a minimization of phase inversion temperature, thereby increasing the ease of emulsification. For systems having co surfactant, separation of components between the oil and aqueous phases, may take place leading to a mechanism described as "Diffusion & Standing" whereby the oil is solubilized, leading to migration into the aqueous phase. [12,13,14]

TYPES OF SEDDS

On the basis of the water solubility of components, SEDDS can be classified as shown in Figure 1.

Figure 1: It shows lipid formulation classification system (LFCS)



(A) Non-water soluble Component Systems

These systems are isotropic mixtures of lipids & lipophillic surfactants having HLB value less than 12 that self emulsify to form fine oil in water emulsion in aqueous medium. Self emulsification is generally obtained at a surfactant level above 25% w/w. But at a surfactant level of 50-60% w/w the emulsification process may be compromised by formation of viscous liquid crystalline gels at the oil/water interface. This system is also known as Type-II SEDDS according to lipid formulation classification System (LFCS). [15]

Poorly water soluble drugs can be incorporated in SEDDS & encapsulated in capsules (hard or soft gelatin) to produce convenient single unit dosage forms. These systems offer advantages -

- They are able to generate large interfacial areas which cause efficient partitioning of drug between oil droplets and the aqueous phase.
- They can overcome the slow dissolution step typically observed with solid dosage forms.

(B) Water soluble component system

These systems are formulated by using hydrophilic surfactants with HLB more than 12 & co solvents such as Ethanol, Propylene Glycol & Polyethylene glycols. Type III SEDDS are commonly known as self micro-emulsifying drug delivery systems (SMEDDS). [16]

Type III formulations can be further divided into type III A & Type III B formulations in order to identify more hydrophilic forms. In Type IIIB, the content of hydrophilic surfactants and co solvents is increased and lipid content is reduced.

The distinction between SEDDS & SMEDDS formulation is commonly based on particle size and optical clarity of resultant dispersion. Thus SEDDS formulations typically provide opaque dispersions with particle size greater than 100 nm while SMEDDS disperse to give small droplets with particle size less than 100 nm and provide optically clear or slightly opalescent dispersions.

SEDDS and SMEDDS have played an important role in the improvement of solubility as well as bioavailability of drugs with poor aqueous solubility. An example of the marketed SMEDDS formulation is Neoral Cyclosporine formulation in which corn oil, derived mono, di and triglycerides were used as lipid phase, cremophor RH 40 as surfactant, propylene glycol & ethanol as co solvent along with α- tocopherol as an antioxidant. [17] Neoral spontaneously forms a transparent & thermo-dynamically stable dispersion with droplet size below 100 nm when introduced into an aqueous medium. [18,19]

SEDDS may be solid or liquid in nature and they may be formulated into tablets, capsules, pellets, solid dispersions, microspheres, nanoparticles or dry emulsions.

EXCIPIENTS USED IN SEDDS FORMULATION

A large number of excipients are used in the formulation of self emulsifying drug delivery systems. Oil along with surfactant are necessary components, however, co surfactants may also be used. Use of other excipients in SEDDS is governed by the type of dosage form. Various types of oils (natural, synthetic or semi synthetic) have been used for the formulation of SEDDS of various drugs. [6] Some examples of the oils used in the marketed preparations are cited in the table 1. Oils used with different drugs for SEDDS formulation are shown in the table 2.

Table 1: Type of oils used in marketed SEDDS

Type of oil	Marketed Product	Drug
Corn oil	Depakene capsule	Valproic acid
Olive oil	Sandimmune oral solution	Cyclosporine
Sesame oil	Marinol soft gelatin capsule	Dronabinol
Soya bean oil	Accutane soft gelatin capsule	Isotretinoin
Peanut oil	Prometrium soft gelatin capsule	Progesterone
Bees wax	Vesanoid soft gelatin capsule	Tretinoin
Hydrogenated soya bean oil	Accutane soft gelatin capsule	Isotretinoin

Table 2: Type of oils used with different drugs in SEDDS

Oil	Drug
Soya bean oil	Probucol,[20] Ibuprofen [21]
Ethyl oleate	Vinpocetine [22]
Oleic Acid	Puerarin [23]
Maisine oil	Lercanidipine [24]
Polyoxy castor oil	Simvastatin [25]
Peanut oil	Griseofulvin [26]

Generally oils with long & medium chain triglycerides with varying degrees of saturation are used for formulation of SEDDS. Edible oils without any modification provide the "Natural" base for lipid vehicles, but their poor ability to dissolve larger amount of drugs & their lower self emulsification efficiency restricts their use in SEDDS. Therefore, modified or hydrolyzed vegetable oils are preferred as compared to Natural edible oils for use in SEDDS formulation. [27-29]

Surfactants

Emulsifiers obtained from natural sources are expected to be safer than synthetic surfactants. As compared to cationic or anionic surfactants, nonionic surfactants are known to be less toxic. Nonionic surfactants with higher HLB value are preferred for formulation of SEDDS however; ethoxylated polyglycolyzed glycerides & tween 80 are the most commonly used surfactants. The concentration of surfactant in self emulsifying systems varies from 30-60% w/w of the formulation in order to prepare & maintain emulsion state in the GIT but higher concentration of surfactant may cause local irritation in the GI tract as well as moderate reversible changes in intestinal wall affecting its permeability. [30, 31] The surfactants being amphiphilic in nature can solubilize higher quantities of hydrophobic drug. Some of the surfactants used in the marketed preparations are given in the table 3. Various surfactant used with drugs in SEDDS are shown in table 4.

Table 3: Type of surfactants used in marketed SEDDS

Surfactant	Marketed Product	Drug
Span 80,Tween 80	Gengraf soft gelatin capsule	Cyclosporine
Tween 20	Targretin Hard gelatin Capsule	Bexarotene
Cremophor RH 40	BCNU self emulsifying implant	Carmustine
D-alpha Tocopheryl Poly ethylene Glycol 1000 Succinate (TPGS)	Agenerase Soft Gelatin capsule, Agenerase oral solution	Amprenavir
Labrafil M 1944 CS	Sandimmune oral solution.	Cyclosporine

Table 4: Type of surfactants used with different drugs in SEDDS

Surfactant	Drug
Tween 80	Ketoprofen, [32] Carvedilol [33]
TPGS	Tacrolimus [34]
Labrafil M 1944 CS	Probucol [20]
Tween 85	Indomethacin [35]
Cremophor EL	Loratadine [36]

Co solvents/Co-surfactants

Generally high surfactant concentrations (usually greater than 30% w/w) are required for formulation of SEDDS. Organic solvents such as ethanol, propylene glycol, glycerol, polyethylene glycol, aids in dissolving large amount of either the drug in hydrophilic surfactants or the lipid base. These solvents also act as co-surfactant in the micro emulsion systems. It has been observed that drug release from the formulation improves with increasing amount of co-surfactant

Alcohol & other volatile solvents used in the conventional self emulsifying formulations migrate into shells of capsules resulting in precipitation of lipophillic drug. Therefore, alcohol free SMEDDS are also being studied. [27] Some of the examples of co-solvents used in marketed formulations are cited in table 5.

Table 5: Type of Co surfactants used in marketed SEDDS

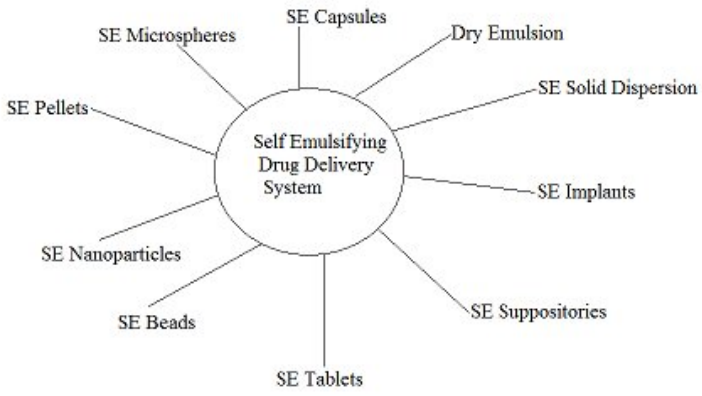
Co surfactants	Marketed preparation
Poly Ethylene Glycol	Targretin soft gelatin Capsule, Gengraf hard gelatin capsule, Agenerase soft gelatin capsule
Glycerin	Sandimmune soft gelatin capsule.
Propylene glycol	Neoral soft gelatin, Neoral oral solution, Gengraf hard gelatin, Lamprene soft gelatin capsule.
Ethanol	Neoral Soft gelatin & Neoral oral, sandimmune soft gelatin & oral sol, gengraf hard gelatin capsule

It has been observed that rapid emulsification occurs at an optimum surfactant concentration of 35% w/w and all systems containing 20-50% w/w Tween 85 emulsify rapidly. If surfactant concentration is more than 50%, viscous gels are formed which reduces self emulsification efficiency. Self emulsifying systems produce very fine dispersion if more energy for dispersion is provided by homogenization. [37]

Solid Self Emulsifying Drug Delivery System (S-SEDDS):-

As SEDDS may exist in liquid or solid dosage form, but due to better stability as well as ease in handling and transportation, solid SEDDS are generally preferred over liquid SEDDS. Conventional solid SEDDS are capsules, solid dispersions and dry emulsions but recently, a number of other solid SEDDS have been prepared such as Pellets, Microspheres, Tablets, Beads, Implants & Suppositories. (Figure 2)

Figure 2: It shows types of solid SEDDS



Self Emulsifying Capsules

Capsule having conventional liquid self emulsifying formulation, upon administration form droplets of micro emulsion spontaneously & then disperse in gastro intestinal tract and yield improved absorption. They however have certain limitations as if irreversible phase separation of microemulsion takes place, then drug absorption decreases. In such cases, to improve the absorption, sodium dodecyl sulphate is added to SE formulations & super-saturable SEDDS is formulated by using a small quantity of polymer in the formulation to prevent drug precipitation by generating & maintaining supersaturated state *in vivo*. These formulations contain a reduced amount of surfactant & minimize any gastrointestinal side effects. In the gastrointestinal tract, capsules disperse to form SES uniformly dispersed to form very fine droplets (in microns) & enhances bioavailability. Another type of SE capsules is solid SES filled into capsule. [38,39]

Dry Emulsion

It is mainly oil in water emulsion, converted into solid by using various techniques such as spray drying, using solid carrier adsorption or freeze drying technique. [40-42] Dry emulsion may be re dispersed in water before use. These are actually powders in which emulsification spontaneously occurs *in vivo* or after exposure to an aqueous solution. Dry emulsion technology not only avoids the use of harmful or toxic organic solvents but effectively removes the stability problems (such as phase separation, creaming & contamination by micro- organism during storage) associated with classic emulsion. MCT (Medium Chain Triglycerides) are generally used as oil phase for these formulations. Dry emulsions can be used for further preparation of tablets & capsules. This technique has been applied for poorly water soluble drug amlodipine. [43]

A new interesting development in this field is newly developed enteric coated dry emulsion formulations which are more appropriate for peptide & protein drugs oral delivery. These formulations are prepared by using surfactant, vegetable oil & pH responsive polymer followed by lyophilization. [44]

SE Solid Dispersion

Solid dispersions had widely being used to increase the dissolution rate and bioavailability of poorly water soluble drugs although stability is a major concern during their manufacturing. S*erajuddin* (1999) reported that these problems can be overcome by using self emulsifying excipients such as Gelucire 44/14, Gelucire 50/02, Labrasol, Transcutol and TPGS. [45-47]

Hot-melt granulation is a widely used technique for the preparation of solid dispersion. *Gupta , et al* prepared SE solid dispersion granules of seven drugs using this technique including four carboxylic acid containing drugs, an amide containing drug (Phenacetin), a hydroxyl containing drug & a drug having no proton donating groups (Progesterone) in which Neusilin US2 was used as surface adsorbent and gelucire 50/13 was used as dispersion carrier. [48]

Self Emulsifying Tablets

First self emulsifying (SE) tablet of ubiquinone was prepared by *S.Nazzal , et al*, for studying effect of formulation ingredients on the release rate of drug & to evaluate an optimized self nano emulsifying tablet formulation. Prepared nano emulsion was adsorbed on granular materials and then compressed to form tablets. The dissolution profile of optimized self emulsifying tablet showed 80-90% drug release in 45 minutes. [49]

Another drug Diclofenac has also been formulated as Self emulsifying tablet using goat fat and Tween 65. [50]

Self Emulsifying Implants

The drug carmustine (BCNU) is a chemotherapeutic agent used to treat malignant brain tumours but has short biological half life. Self emulsifying implant was prepared by using tributyrin, cremophor RH 40 & Labrafil 1944 in order to increase the stability of drug and compared its release from PLGA (Poly d, l/lactide co-glycolide) water implants, fabricated into wafers with a flat & smooth surface by compression moulding. It was observed that the *in vitro* half life of BCNU increased upto 130 minutes as compared to 45 minutes with intact BCNU. [51] Such wafers had higher *in vitro* anti tumour activity & were less susceptible to hydrolysis than wafers without SES.

Loomis et al patented another type of co-polymers for implantable prostheses. These co polymers were having hydrophilic region, bioresorbable region & at least two cross-linkable functional groups in a single polymer chain. Such copolymers have properties of self emulsification without requiring any emulsifier and can be used as good sealants for implantable prostheses. [52]

Self Emulsifying Suppositories

Some investigators have observed that solid SEDDS can not only increase GI adsorption but can also be used to enhance rectal and vaginal absorption. Glycyrrhizin given by oral route does not achieve therapeutic plasma concentration but satisfactory therapeutic levels can be achieved by the use of either rectal or vaginal SE suppositories for the treatment of chronic hepatitis. Indomethacin suppositories have also been prepared by using self emulsifying technique. [35]

Self Emulsifying Beads

In SE systems, solid dosage forms can be developed by using less amount of excipient i.e. by formation of Beads. *Paradkar & Patil* used solvent evaporation technique for deposition of SE system into micro porous polystyrene beads.

Porous polystyrene beads are having complex internal void structures. These beads are produced by copolymerization of monomers styrene and divinyl benzene. It is chemically inert, biocompatible and stable over a wide range of pH, temperature & humidity. Geometrical features of porous materials like bead size & pore architecture governs the loading efficiency and *in vitro* drug release from SES loaded porous poly styrene beads. [36]

Self Emulsifying Nanoparticles

Self emulsifying nanoparticles can be prepared by using various techniques. One of the techniques is solvent injection method in which molten lipid mass containing lipid, surfactant & drug is injected drop wise into a non-solvent system. Larger particles are removed by filtration and then filtrate is dried to get nanoparticles. By this method, self emulsifying nanoparticles using biodegradable homolipid with particle size of approximately 100nm are obtained with loading efficiency of 70-75%. [53]

Another technique is sonication emulsion-diffusion-evaporation which allows the loading of both 5-Flourouracil (5–FU) and antisense Epidermal Growth Factor Receptor (EGFR) plasmid in biodegradable PLGA/o-CMC nanoparticles. This combination i.e. PLGA & o-carboxymethyl chitosan shows self emulsifying effect without any surfactant stabilizer. [54] It was found that the release rate of 5-FU from self emulsifying nanoparticles was sustained for as long as three weeks.

Trickler et al used multiple emulsion (o/w/o) solvent evaporation method for preparation of self emulsifying nanoparticle system with chitosan and glyceryl monooleate (GMO) for the delivery of paclitaxel. These nanoparticles possessed bioadhesive properties & increased cellular association of the drug. [55]

Sustained Released Solid Self Emulsifying Drug Delivery System

(1) Self Emulsifying Microspheres

You et el, formulated solid SE sustained release microspheres using Zedoary Turmeric oil (ZTO), a traditional Chinese Medicine (TCM), as oily phase. ZTO has potent pharmacological actions such as tumour suppression, antibacterial & antithrombotic activity. Quasi emulsion solvent diffusion method involving spherical crystallization was used for the preparation. The plasma concentration obtained after oral administration to rabbits showed the BA of 135.6% compared with conventional SEDDS i.e. liquid SEDDS. [56]

(2) Self emulsifying sustained release tablets

A gelled SEDDS has been developed by *Patil, et al* using colloidal silicon dioxide as gelling agent in order to minimize the amount of solidifying excipients required for conversion of liquid SEDDS into solid SEDDS. Colloidal SiO_2 reduces the amount of required solidifying excipients & aids in sustaining release rate of drug. [32]

Self Emulsifying (SE) tablet increase the penetration capacity of indomethacin through GI tract mucosal membrane.SE tablets were prepared by using glycerol monolaurate & tyloxapol (a copolymer of alkyl phenol & formaldehyde). [57]

A recent advance development in SE tablets is SE osmotic pump tablet of carvedilol. In this tablet, osmotic pump system [58] is chosen as a carrier for SE system and is able to provide excellent features like stable plasma concentration, a controllable drug release rate and bioavailability of 156.8% relative to conventional carvedilol tablets.

(3) Self emulsifying controlled release pellets

Pellets are the multiple unit dosage forms which possess a number of advantages over conventional solid dosage forms like ease of manufacturing, reduce the intra & inter subject variability of plasma profiles and also reduce GI irritation without lowering drug bioavailability. [59] SE controlled release pellets were prepared using extrusion/ spheronization by *Serratoni , et al* by incorporating drugs into SES for enhancing the release rate of drug and coating the pellets with a water insoluble polymer to control the release rate. It revealed that a combination of coating & self emulsification could effectively control *in vitro* release of drug and a range of release rates can be obtained. [60] In another study glyceryl palmito-stearate (Gelucire 54/02) & glyceryl behenate (Gelucire 70/02) were used for preparation of matrix sustained release pellets. [61]

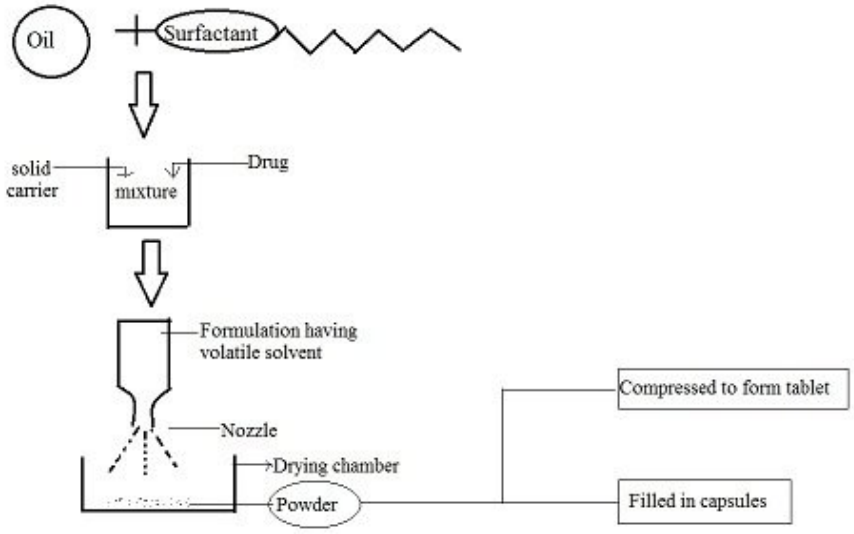
Methods of solidification

There are number of techniques for transformation of liquid & semi-solid SE formulations into solid SEDDS. These techniques are spray drying, spray cooling, melt extrusion, melt granulation, adsorption on to solid carriers and super critical fluid based method. High pressure homogenization has also been used to produce solid lipid nanoparticles or nanostructured lipid carriers.

Spray Drying

In this technique, first of all formulation having oil, surfactant, drug and solid carrier are sprayed into a drying chamber through a nozzle. The volatile vehicles evaporate leaving behind small solid particles which may be compressed into tablets or filled into capsules. The technique is shown in figure 3. This technique has been used to prepare dry emulsions by removing water from an ordinary emulsion. Nimodipine self micro emulsifying formulation has been prepared by spray drying technique using dextran as a solid carrier. [62] This technique has also been applied for development of self emulsifying curcumin [63] and dexibuprofen. [64]

Figure 3 – It shows spray drying technique



Spray cooling

The technique spray cooling is also known as spray congealing, where, the molten formulation is sprayed into a cooling chamber. When this molten mixture comes in contact with cooling air, the molten droplets congeal & recrystallize into spherical solid particles which collect into the bottom of the chamber as fine powder. The fine powder may then be used for development of solid dosage from such as capsules, tablets etc.

To atomize the liquid mixture & to generate droplets, different atomizers can be used but ultrasonic atomizer is most preferred. The excipients used with this technique are polyoxyl glycerides specially steroyl polyoxyl glycerides, gelucire 50/13. [1] Praziquantel [65] & diclofenac [66] SEDDS have been prepared by using spray cooling technique.

Melt Extrusion/Extrusion Spheronization

Extrusion Spheronization technique is based on the property of materials which can be easily extruded and spheronized. These techniques do not require liquid excipients although constant temperature and pressure has to be maintained to achieve high drug loading. Melt extrusion ensures content uniformity & is widely used method for preparing pellets and granules. In extrusion, raw materials with plastic properties are converted into uniform pellets of varying size which depend on size of extruder aperture.

Self nanoemulsifying formulation of ubiquinone has been formulated by using extrusion Spheronization technique. [49] The bioavailability of propranolol has also been improved by using this technique. [67] Self emulsifying pellets & bilayered cohesive self emulsifying pellets of diazepam have also been prepared by extrusion spheronization technique. [68, 69]

Melt Granulation

Melt granulation is a one step process, where, powder agglomerates are obtained by adding binder that melts or softens at low temperature. Melt granulation is also known as “thermoplastic pelletization.” It is used for those excipients that exhibit thermoplastic properties. A large range of solid & semi-solid lipid can be used as a binder for solid dispersions prepared by melt granulation whereas, lipids with a low HLB & high melting point are suitable for sustained release formulations. Semi-solids with high HLB are used for immediate release and bioavailability enhancement. Gelucire, a lipid based excipient, is able to further increase the

dissolution rate as compared to poly ethylene glycol because of its self emulsifying ability. [70] Gelucire 44/14 has high HLB value of 14 and possesses good self emulsifier property. [71]

Other lipid based excipients used for solid SES are lecithin, partial glycerides and polysorbates (tweens). Melt Granulation process is used for adsorbing SES into solid carriers like silica & magnesium alumino meta-silicate. [72] The parameters that control granulation process are the impeller speed, mixing time, viscosity and particle size of binder.

Super Critical Fluid Technology

The most commonly used super critical fluid is super critical carbon dioxide. [73, 74] The lipid materials may be used in super critical fluid technology either for preparing solid dispersion or for coating of drug particles. In this technique drug & lipid excipients are dissolved in an organic solvent such as methanol & then in a supercritical fluid. [75-77] Generally, the coating process involves dispersing the drug particles in the super critical fluid containing coating material. Initially, the solubility of coating material is sustained by elevated temperature & pressure and then coating is facilitated by a gradual decrease in pressure & temperature which decreases the solubility of the coating material in the supercritical fluid leading to its gradual deposition onto drug particles. Lipid based excipients used for preparation of controlled release formulation are glyceryl trimyristate (dynasan 114) and stearoyl poly oxyl glycerides (gelucire 50/02). [73,74]

In pharmaceutical industry, this technique has been successfully applied for bioavailability improvement of carbamazepine using vitamin E, TPGS & Gelucire 44/14. [74-77] However, following points must be considered while using this technique –

- The integrity/stability of the active substance under the process conditions.
- The solubility of the formulation components in the supercritical fluid.
- The energy requirement or environmental conditions relating to evaporation of solvents.
- Economic considerations as this method have lower drug loading capacity and should be used for highly potent & low dose drugs.

Solid-Lipid Nanoparticles (SLN) and Nano Structured Lipid Carriers (NLC)

SLN and NLC have size in the range 50-1000 nm and differ in state of core as SLN have a solid core while NLC have a liquid core. In the preparation of SLN, drug is dissolved in aqueous solution of the surfactants & then high pressure homogenization of the solid matrix & drug solution is carried out.

NLC are reservoir system derived from SLN to increase the drug loading capacity of system. In addition to the classic SLN components, NLC also contain liquid lipid excipients such as MCT (medium chain triglycerides). They have been mainly used for controlled release formulations via the oral, [78] I.V. [79] or topical Route. [80]

The advantages of SLN are that they can be prepared without use of organic solvents & with a wide range of lipid excipients. Coenzyme 10 has been formulated as an NLC using caprylic/capric triacyl glycerols as liquid lipid as carriers. [81]

Clozapine SLN have been formulated by the use of soya lecithin 95%, Poloxamers 188, triglycerides (such as trimyristin, tripalmitin & tristearin) and Stearylamine as a positive charge inducer by hot homogenization followed by ultrasonication. [82]

EVALUATION OF SEDDS

A number of tests are carried out for characterization and evaluation of SEDDS.

1. Dispersibility Test

The dispersibility test of SEDDS is carried out to assess its capability to disperse into emulsion and the size of resulting globules to categorize them as SNEDDS. It is carried by using a standard USP dissolution apparatus 2 (Paddle Type). [11,83] 1 ml of each formulation is added to 500 ml of water at 37 $\pm$ 0.5 ^{o}C and the paddle is rotated at 50 r/ min. On titration with water the SEDDS formulation forms a mixture or gel which is of different type (given in table 6) depending upon which the *in vitro* performance of formulation can be assessed. [84]

Table 6: Type of formulation depending upon visual observation

Mixture/Gel	Type of formulation
Transparent mixture	Micro emulsion
Transparent Gel	Micro emulsion gel
Milky or cloudy mixture	Emulsion
Milky Gel	Emulgel

The stability of the formulation decreases from micro emulsion to emulgel.

2. Rheological Properties Determination

The SEDDS system can also be administered in soft gelatin capsules, where, it should have appreciable flow properties for processing. The rheological properties (viscosity, flow, thixotropy, static yield, creep value) of formulation (diluted to 5 % v/v water) are determined by rotational viscometers, digital instruments coupled with either cup and bob or coaxial measuring device. [85,86] A type of rotational viscometer has also been used for determination of viscosity of fresh as well as other SEDDS formulations which has been stored for longer duration of time. [87] Viscosity determination of liquid SEDDS also indicates whether the system is o/w or w/o, as low viscosity systems are o/w and high viscosity systems are usually w/o in nature. Viscosity of formulation is inversely proportional to dilution.

3. Thermodynamic stability studies

The physical stability of a 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 & gelatin shell of capsule (if formulation filled in capsule) may cause brittleness, softness and delayed disintegration or incomplete release of drug. The following cycles are carried out for these studies-

i) Heating cooling cycle: - Six cycles of cooling and heating between refrigerator temperature (4°C) and elevated temperature (45°C) with exposure at each temperature for not less than 48 hours are carried. Those formulations, which are stable, are then subjected to centrifugation test. [83]

ii) Centrifugation: - Formulations which pass the heating cooling cycle are centrifuged at 3500 r/ min for 30 min. Those formulations that doesn't show any phase separation are taken for the freeze thaw stress test.

iii) Freeze thaw stress cycle:- Three freeze thaw cycles b/w -21° C & 25° C with storage at each temperature for not less than 48 hours. [26, 83] Those formulations which pass this test show good stability with no phase separation, cracking or creaming. The formulations that pass this test are then further taken for dispersibility test for assessment of self emulsification efficiency. [69,88,89]

4. Robustness to dilution

Emulsions upon dilution with various dissolution media should not show any phase separations or precipitation of drug even after 12 hrs of storage, that formulation is considered as robust to dilution. [90-94]

5. Turbidimetric Evaluation

Turbidity is a parameter for determination of droplet size and self emulsification time. Fixed quantity of SEDDS is added to fixed quantity of suitable medium (0.1 N HCL or Phosphate Buffer) under continuous stirring at 50 r/ min on magnetic stirrer at optimum temperature and the turbidity is measured using a turbidimeter. Since the time required for complete emulsification is too short, it is not possible to monitor the rate of change of turbidity i.e. rate of emulsification. [85, 86] Turbidimetric evaluation is carried out to monitor the growth of droplet after emulsification.

6. Droplet size Analysis & Particle size Measurements

Photon correlation Spectroscopy (PCS) or dynamic light scattering (DLS) or Laser Diffraction Techniques are used to determine droplet size of emulsion. A number of equipments are available for measurement of particle size viz. Particle Size Analyzer, Mastersizer, Zetasizer etc which are able to measure sizes between 10 and 5000 nm. In many instances nanometric size range of particle is retained even after 100 times dilution with water which indicates the system's compatibility with excess water. [85, 86]

7. 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 formulations is introduced into 250 ml of 0.1N HCL or 0.5% SLS solution. The time for emulsification at room temperature is indicated as self emulsification time for the formulation. [90]

8. Zeta Potential Determination

The stability of emulsion is directly related to the charge present on mobile surface, which is termed as zeta potential. Zetasizer, Mastersizer etc are often used to determine zeta potential. The Zetasizer uses light scattering techniques to determine globule size, zeta potential and molecular weight of nanoparticulate systems. The instrument determines size and zeta potential for optimization of stability and shelf life and speeding up the formulation development The SEDDS formulation is generally diluted in a ratio of 1: 2500 (v/v) with distilled water with constant stirring for determination of zeta potential. [95]. Zeta potential is calculated according to Helmholtz-Smoluchowski equation-

$$U=\varepsilon\xi Ex/\mu$$

U =Electrophoretic velocity ε = permittivity ξ = Zeta potential

μ = Viscosity Ex = Axial electric field

9. In vitro Diffusion Study

This study is done to determine release behavior of formulation using dialysis technique where phosphate buffer (pH 6.8) is generally used as dialysing medium. One end of the dialysis membrane is tied with a thread and 1 ml of the SEDDS formulation along with 0.5 ml of dialysing medium are filled in the membrane. The other end of membrane is also tied with thread and then allowed to rotate in dialyzing medium at 100 *r/ min* using magnetic stirrer or dissolution apparatus. Samples are withdrawn at different time intervals and then after suitable dilution are analyzed. Volume of samples withdrawn is replaced with fresh dialysing medium. [32]

10. In vitro Dissolution Technique

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 (Sodium Lauryl Sulphate) at 50 r/ min and maintaining the temperature at 37 $\pm$ 0.5 ^{o}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. [84]

11. Liquefaction time

This test is done to determine the time required by solid SEDDS formulation to melt *in vivo* in the absence of agitation in simulated gastric fluid. The formulation is packed in a transparent polyethylene film and tied to the bulb of thermometer. [50] The thermometer is then placed in round bottom flask in which simulated gastric fluid without pepsin is filled. The temperature is maintained at 37$\pm$ 0.5 ^{o}C by using heating mantle.

12. Refractive Index (R.I.) & Percent transmittance

Refractive Index & percent transmittance are determined to check the transparency of formulation. Refractive Index of the formulation is measured by refractometer by placing drop of solution on slide & then compare it with water (R.I = 1.333). The percent transmittance of the formulation is measured at a particular wavelength using UV spectrophotometer by using distilled water as blank. [6] If R.I. of formulation is similar to that of water & formulation having percent transmittance is greater than 99%, then the formulation are transparent in nature.

13. Permeation studies

For information about oral bioavailability enhancement of a formulation, one must have to perform *in vitro* or *ex vivo* studies. For these studies, isolated and perfused organ systems have been developed. [95] These organ systems have the advantage that research scientist works with an intact organ, where physiological cells remain in contacts intracellular matrices are preserved. [96] A number of techniques are available for such *in vitro* studies First is In Situ Single Pass Perfusion Technique (SPIP) in which perfusion solution is passed through the jejunum(a part of intestine) and the experimental conditions provided are closer to the *in vivo* conditions. This technique is also able to determine exact absorption mechanism that is passive or active or carrier mediated absorption. [97] Permeability parameters are determined by calculating the amount of drug which is not absorbed from intestine. [98]

Second technique is Everted sac technique in which a small part of intestine (2-4 cm) is tied at one end and everted using a glass rod or thread. The technique is used to determine kinetic parameters. [99] In the presence of sensitive detection methods (such as radiolabelled compounds), drug transport across the intestine and through the epithelial cells can be studied. [100] The method is suitable for calculating absorption at different sites in small intestine and estimating the first pass metabolism of xenobiotics in

intestinal epithelial cells. [99,101] The limitation of this technique is that muscularis mucosa is present which is usually not removed from everted sac preparations. That is why this method is not preferred for accurate determinations.

Third technique is Diffusion cell technique in which diffusion across a small part of intestine or any other tissue (such as buccal, rectal, skin, lung, gastric) is studied using the media with specific pH and temperature conditions. On both sides of diffusion membrane, buffer solution is continuously gassed with carbogen. [99]

APPLICATION OF SEDDS

Improvement in solubility & Bioavailability

In SEDDS, the lipid interacts readily with water leading to formation of fine o/w emulsion. The droplets of emulsion deliver the drug to G.I tract in the dissolved state which can be easily absorbed. There are number of examples (shown in table 7) of drugs for which improved bioavailability have been reported by their SEDDS formulations

Table 7: Literature reports on bioavailability enhancement using SEDDS.

Drug	Bioavailability enhancement
Simvastatin	1.5 folds [25]
Carvedilol	3-4 folds [84]
Phenytoin	2.3 folds [85]
Acyclovir	3.5 folds [91]
Halofantrine	6-8 folds [102]
Gentamycin	5 folds [103]
Ketoprofen	1.13 folds [104]
Vinpocetine	17.3 folds [105]
Vitamin A	2 folds [106]
Exemestane	2.9 folds [107]

Supersaturable SEDDS (S-SEDDS)

S-SEDDS formulations have a reduced level of surfactant along with a polymeric precipitation inhibitor which stabilizes the drug in a super saturated state. HPMC & other cellulose polymers are used to inhibit crystallization and maintain supersaturated state of drug for longer duration. S-SEDDS are developed to reduce the side effects of surfactants & to achieve rapid absorption of poorly soluble drug because high surfactant level may cause GI irritation. [39] It has been noticed that the significantly reduced amount of surfactant used in the S-SEDDS formulation provides a better toxicity/safety profile than the conventional SEDDS formulation. The mechanism of inhibited crystal growth and stabilization of super saturation by means of polymers needs further explanation. [39,108,109] In salicylic acid [109] and docetaxel [110] SEDDS formulation, HPMC is used as precipitation inhibitor. A five fold increase in bioavailability has been observed with PNU-91325 when HPMC in place of propylene glycol, is used as precipitation inhibitor. [111]

Protection against Biodegradation

Many drugs are degraded in physiological system due to acidic pH in stomach, enzymatic or hydrolytic degradation. In GI tract, acetylsalicylic acid undergo hydrolysis to generate salicylic acid in an acidic environment, but the drug is protected from such degradation when formulated in a galacticles oral lipid matrix system (self emulsifying system), showing good plasma profile as compared to the commercial formulation. [112]

Liquid Crystalline Nanoparticles (LCNPs) are very good solubilizers for sparingly soluble drugs & show high drug carrying capacity. Proteins and peptides can be protected from biodegradation by formulating LCNPs. For water soluble peptides, bioavailability enhancement may vary from 20 to 100 times. [6] LCNPs can be used for controlled release as well as drug targeting. LCNP carriers can also be manipulated for targeted release at different absorption sites e.g. in lower or upper intestine.

SEDDS for Herbal Drugs and Traditional Medicine

A number of herbal drugs and traditional medicines are being exploited for development of SEDDS as many of them are either extracts or contain volatile and fixed oils. Silybin obtained from *Carduus marianus* is found to be effective in protecting liver cells from harmful effects caused by drinking, smoking, overworking, stress, environmental pollutants or drugs that cause liver damage. Silybin has low oral bioavailability because of its low aqueous solubility. SEDDS formulation of Silybin has increased its oral bioavailability by at least 4 folds. [113]The extracts of *Ginkgo biloba* have antioxidant, antiischaemic, neuroprotectant, cardiovascular and cerebrovascular activities & have beneficial effects on cognitive deficits including Alzheimer's disease & multi infarct dementia [114]. The solubility of active components of *Ginkgo biloba* is less. Its SEDDS formulation increased the dissolution & improved oral absorption and achieved the reproducible blood time profiles of active component. [115]

Curcuma Zedoaria (Zingiberaceae) also known as Er-zhu contains Zedoary Turmeric oil (ZTO), an essential oil extracted from dry rhizome. The therapeutic activities of the ZTO are suppression of tumours, anti bacterial and antithrombotic activity besides increasing white blood cell count & gastric motility. To increase the *in vivo* absorption of ZTO, self emulsifying microspheres were developed using quasi emulsion solvent diffusion method. The ingredients of the system were hydroxy propyl methyl cellulose acetate succinate (HPMCAS-LG), talc & aerosil 200, phosphate buffer (pH 6.8). The release rate of ZTO from microspheres was enhanced significantly with increasing amounts of dispersing agents & the efficiency of self emulsification closely related to HPMCAS-LG/Aerosil 200 ratio. The emulsion droplets released from microspheres were much smaller than those of conventional SEDDS. [56]

Another Chinese plant *Fructus Schisandral Chinensis (*Wurenchun) has also been formulated as SEDDS for improved solubility and bioavailability. This plant is useful in lowering abnormal serum glutamic pyruvic transaminase (SGPT) level of patients suffering from acute or chronic hepatitis. [116]

CONCLUSION

Self emulsifying Drug Delivery Systems are actually mixtures of 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 take water from its surrounding environment and spontaneously form oil in water emulsion which disperse into fine droplets. The finer droplets provide higher surface area for the drug

to dissolve or permeate in surrounding medium. SEDDS are prepared generally in liquid dosage forms but solid SEDDS (tablets, capsules, beads, microspheres etc.) are preferred due to ease in handling, transportation and better stability.

Despite the advances made with the arrival of newer surfactants, co-solvents and lipids, the potential of SEDDS has not been effectively utilized and requires more attention of formulation scientist. Absence of suitable *in vitro* models explaining the state (whether dissolved or not) in G.I.T (*in vivo)* for evaluation of SEDDS are 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 bioavailability of BCS class II and IV drugs as well as for therapeutic application of various herbal drugs.

REFERENCES

[1] S. Katteboina, P. Chandrasekhar, S. Balaji. Approaches for the development of solid self-emulsifying drug delivery systems and dosage forms. Asian J Pharm Sci., 2009, 4: 240-253.

[2] M.Sugimoto, T. Okagaki , S.Narisawa , *et al*. Improvement of dissolution characteristics & bioavailability of poorly water soluble drugs by novel co-grinding method using water soluble Polymer. Int. J. Pharm 1998, 160: 11-19.

[3] C.H. Perng, A.S.Kearney, K. Patel, *et al.* Investigation of formulation approaches to improve the dissolution of SB-210661, a poorly water soluble 5-lipooxygenase Inhibitor. Int. J. Pharm., 1998, 176: 31-38.

[4] S.Nazzal, N. Guyen , I.K.Reddy , *et al*. Preparation and Characterization of Coenzyme Q_{10} eudragit solid dispersion. Drug Dev. Ind. Pharm., 2002, 28 : 49-57.

[5] S. Jessy, J. Diagambar . Newer approaches to self emulsifying drug delivery system. Int. J. Pharm. and Pharm. Sci. 2010, 2 : 37-42.

[6] P.A.Patel, G.M.Chaulang, A. Akolkotkar , *et al*. Self Emulsifying Drug delivery system: A Review. Res. J Pharm and Tech., 2008, 1: 313-323.

[7] N.S.Barakat. Enhanced Oral bioavailability of Etodolac by SEDDS: *In vitro* and *in vivo* evaluation. J. Pharm. Pharmacol., 2010, 62 :173-180.

[8] M.E. Perlman, S.B. Murdande, M.J. Gumkowski , *et al*. Development of a self emulsifying formulation that reduces the food effects for torcetrapib. Int. J. Pharm.,2008, 351: 15-22.

[9] H. Reiss. Entropy induced dispersion of bulk liquids. J. Colloids interface sci. 1975, 53: 61-70.

[10] M. J. Groves, R. M. A. Mustafa, J.E. Carless. Phase studies of mixed phosphated surfactants, n-hexane and water. J. Pharm. Pharmacol., 1974, 26: 616-623.

[11] C.W. Pouton. SEDDS: Assessment of Efficiency of emulsification. Int J Pharm 1985, 27: 335-348.

[12] C. W. Pouton. Formulation of self emulsifying drug delivery systems. Adv. Drug Del. Rev., 1997, 25: 47-58.

[13] C. W. Pouton. Study of self emulsifying oil/surfactant mixtures. University of London 1982, 52-62.

[14] C.W. Pouton. Lipid formulations for oral administration of drugs: Non-emulsifying, self emulsifying and self micro-emulsifying drug delivery system. Eur. J. Pharm. Sci., 2000, 11: 593-598.

[15] J.F. Cuine, C. L. Mcevoy, W. N. Charman , *et al*. Evaluation of the impact of surfactant digestion on the bioavailability of danazol after oral administration of lipidic self emulsifying formulations to dogs. J. Pharm. Sci., 2008, 97: 995-1012.

[16] T. Gershanik, S. Benita. Self dispersing lipid formulations for improving oral absorption of lipophillic drugs. Eur. J. Pharm. Biopharm., 2000, 50: 179-188.

[17] R.G. Strickley. Solubilizing excipients in oral and injectable formulations. Pharm. Res., 2004, 21(2): 201-230.

[18] L. Rodriquez, S. Passerini, C. Cavallari , *et al*. Description and Preliminary evaluation of a new ultrasonic atomizer for spray congealing process. Int. J. Pharm., 1999, 183: 133-143.

[19] T.R. Kommuru, B. Gurley, M.A. Khan , *et al*. Self emulsifying drug delivery systems of Coenzyme Q10 formulation development & bioavailability assessment. Int. J. Pharm. 2001, 212: 223-246.

[20] A. Zaghloul, I. Khattab, A. Nada , *et al*. Preparation, characterization and optimization of Probucol self-emulsified drug delivery system to enhance solubility and dissolution. Pharmazie, 2008, 63: 654-660.

[21] A. Mercuri, A. Passalacqua, M. S. Wickham , *et al*.The effect of composition and gastric conditions on the self-emulsification process of Ibuprofen-loaded self-emulsifying drug delivery systems: a microscopic and dynamic gastric model study. Pharm. Res., 2011, 28: 1540-1551.

[22] S.X.Cui, S.F. Nie, L. Li , *et al*.Preparation and evaluation of self micro emulsifying drug delivery system containing Vinpocetine. Drug Dev. Ind. Pharm. 2009, 35:603-611.

[23] D.Q. Quan, G.X. Xu. Formulation optimization of self-emulsifying preparations of Puerarin through self-emulsifying performances evaluation *in vitro* and pharmacokinetic studies *in vivo.* Yao Xue Xue Bao, 2007, 42: 886-891.

[24] N. Parmar, N. Singla, S. Amin , *et al*. Study of co-surfactant effect on nanoemulsifying area and development of Lercanidipine loaded (SNEDDS) self nanoemulsifying drug delivery system. Colloids Surf B: Biointer., 2011, 86: 327-338.

[25] B. K. Kang, J. S. Lee, S. K. Chon , *et al*. Development of self-micro emulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of simvastatin in beagle dogs. Int. J. Pharm., 2004, 274: 65-73.

[26] K. C. Ofokansi, K. I. Chukwu, S.I. Ugwuanyi. The use of liquid self-micro emulsifying drug delivery systems based on peanut oil/tween 80 in the delivery of Griseofulvin. Drug Dev. Ind. Pharm., 2009, 35: 185-191.

[27] P. P. Constantinides. Lipid micro emulsions for improving drug dissolution & oral absorption: Physical & Biopharmaceutical aspects. Pharm. Res. 1995, 12: 1561-1572.
[28] M. Kimura, S. Miwa, M. Kazuyo *, et al*. Relationship between molecular structure & emulsification properties of edible oils. Biosci. Biotech. Biochem., 1994, 58:1258-1261.
[29] D. J. Hauss, S.E. Fogal, J. V. Ficorilli *, et al*. Lipid based delivery systems for improving bioavailability & lymphatic transport of a poorly water soluble LT B_4 inhibitor. J. Pharm. Sci., 1998, 87: 164-169
[30] M.G. Warkerly, C. W. Pouton, B. J. Meakin *, et al*. Self emulsification of vegetable oil nonionic surfactant mixture. ACS Symp. Ser., 1986, 311:242-255.
[31] E. S. Swenson, W. Milisen, W. Curatolo. Intestinal Permeability enhancement, efficacy, acute local toxicity and reversibility. Pharm. Res., 1994, 11:1132-1142.
[32] P. Patil, P. Joshi, A. Paradkar. Effect of formulation variables on preparation & evaluation of Gelled SEDDS of Ketoprofen. AAPS Pharm. Sci. Tech., 2004, 5:e42.
[33] L. Wei, P. Sun, S. Nie *, et al*. Preparation and evaluation of SEDDS and SMEDDS containing Carvedilol. Drug Dev. Ind. Pharm., 2005; 31:785-794.
[34] Y. Wang, J. Sun, T. Zhang *, et al*. Enhanced oral bioavailability of Tacrolimus in rats by self-micro emulsifying drug delivery systems. Drug Dev. Ind. Pharm., 2011, 37: 1225-1230.
[35] J. Y. Kim, Y.S. Ku. Enhanced absorption of Indomethacin after oral or rectal administration of a self emulsifying system containing Indomethacin to Rats. Int. J. Pharm., 2000, 194: 81-89.
[36] P. Patil, A. Paradkar. Porous polystyrene beads as carriers for Self emulsifying system containing Loratadine. AAPS Pharm Sci. Tech., 2006, 7:E 28
[37] J. Patel, A. Shah. Self Emulsifying Delivery systems for poorly absorbed drugs. Int. J. Pharm. Sci. Nanotech., 2008, 1: 123-128.
[38] P. Gao, W. Morozowich. Development of Supersaturable self emulsifying drug delivery system formulations for improving the oral absorption of poorly soluble drugs. Expert Opin. Drug Del., 2006, 3: 97-110.
[39] P. Gao, B.D. Rush, W.P. Pfund. Development of S-SEDDS formulation of Paclitaxel with improved oral bioavailability. J. Pharm. Sci., 2003, 92: 2386-2398.
[40] J. Bamba, G. Cave G, Y. Bensouda, *et al*. Cryoprotection of emulsion in freeze drying: freezing process analysis Drug Dev. Ind. Pharm., 1995, 21: 1749-1760.
[41] K. L. Christensen, G.P. Pedersen, H. G. Kristensen. Technical optimization of redispersible dry emulsion. Int. J. Pharm., 2001, 212: 195-202.
[42] T. Hansen, P. Holm, K. Schultz. Process characteristics & compaction of spray dried emulsions containing a drug dissolved in lipid. Int. J. Pharm., 2004, 287: 55-66.
[43] D.J. Jang, E.J. Jeong, H. M. Lee, *et al*. Improvement of bioavailability & photo stability of amlodipine using redispersible dry emulsion. Eur. J. Pharm. Sci., 2006, 28:405-411.
[44] E. Torrisaka, M. Hashida, N. Kamiya. An enteric coated dry emulsion for oral Insulin delivery. J. Control Rel., 2005, 107:91-96.
[45] A.T. Serajuddin. Solid dispersion of Poorly Water soluble Drugs: early promises, subsequent problems & recent breakthroughs. J. Pharm. Sci., 1999, 88: 1058-1066.
[46] M. Vasanthavada, A.T. Serajuddin. Lipid based self emulsifying solid dispersions. In Oral lipid based formulations: Enhancing bioavailability of Poorly Water Soluble drugs (Hauss DJ. ed*.) pp informa Healthcare,* 2007, 149-184.
[47] A.T. Serajuddin, P.C. Sheen, D. Mufson, *et al*. Effect of vehicle amphliphilicity on the dissolution and bioavailability of a poorly water soluble drug from solid dispersions. J. Pharm. Sci., 1998, 77: 414-417.
[48] M.K. Gupta, Y. C. Tseng, D. Goldman, *et al*. Hydrogen Bonding with Adsorbent during storage governs drug dissolution from solid dispersion granules. Pharm. Res., 2002, 19: 1663-1672.
[49] S. Nazzal, M. Nutan, A. Palamakula, *et al*. Optimization of a self nano emulsified tablet dosage form of ubiquinone using Response surface Methodology: Effect of Formulation Ingredients. Int. J. Pharm., 2002, 240: 103-114.
[50] A.A. Attama, I.T. Nzekwe, P.O. Nnamani, *et al*. The use of solid self emulsifying system in the delivery of diclofenac. Int. J. Pharm., 2003, 262: 23-28.
[51] G. S. Chae, J. Lee, S.H. Kim, *et al*. Enhancement of the stability of BCNU using self emulsifying drug delivery systems and *in vitro* antitumor activity of self emulsified BCNU-loaded PLGA Wafer. Int. J. Pharm., 2005, 301: 6-14.
[52] G. Loomis, N. J. Morristown. Bioresorbable composition for implantable prostheses. US patent number 60281.
[53] A. A. Attama, M.O. Nkemnele. *In vitro* evaluation of drug release from self emulsifying drug delivery systems using a biodegradable homolipid from *Capra Hircus.* Int. J. Pharm., 2005, 304: 4-10.
[54] Y.X. Hu, J. Chang, Y. Guo, *et al*. Preparation and evaluation of 5-FU/ PLGA/Gene nanoparticles. Key Eng. Mat., 2005, 288-289: 147-150.
[55] W.J. Trickler, A.A. Nagvekar, A.K. Dash. A novel nanoparticle formulation for sustained Paclitaxel delivery. AAPS Pharm. Sci. Tech., 2008, 9: 486–493.
[56] J. You, F.D. Cui, Q. P. Li, *et al*. A Novel formulation design about water insoluble oily drug: Preparation of ZTO microspheres with self emulsifying ability & evaluation in Rabbits. Int. J. Pharm., 2005, 288: 315-323.
[57] S. Joseph. Solid self emulsifying dosage form for improved delivery of poorly soluble hydrophobic compounds and the process for preparation thereof. US patent no. 20030072798.
[58] L. L. Wei, S. Nie, W. Pan, *et al*. Investigations of a Novel Self Emulsifying osmotic pump tablet containing carvedilol. Drug Dev. Ind. Pharm., 2007, 33: 990-998.
[59] R. Gandhi, C. L. kaul, R. Panchagnula. Extrusion and Spheronization in the development of oral-controlled release dosage forms. Pharm. Sci. Tech. Today, 1999, 4: 160-170.
[60] M. Serratoni, M. Newton, S. Booth, *et al*. Controlled drug release from pellets containing water insoluble drugs dissolved in a self emulsifying system. Eur. J. Pharm. Biopharm., 2007, 65: 94-98.
[61] J. Hamdani, A. J. Moes, K. Amighi. Physical & Thermal characterisation of Precirol and compritol as lipophillic glycerides used for preparation of controlled release matrix pellets. Int. J. Pharm., 2003, 260: 47-57.

[62] T.Yi, J. Wan, H. Xu, *et al*. A new solid self micro emulsifying formulation prepared by Spray drying to improve the oral bioavailability of poorly water soluble drugs. Eur. J. Pharm. Biopharm., 2008, 70: 439-444.
[63] Y. D. Yan, J. A. Kim, M. K. Kwak, *et al*. Enhanced oral bioavailability of curcumin via a solid lipid based self emulsifying drug delivery system using a spray drying technique. Biol. Pharm. Bull., 2011, 34: 1179-1186.
[64] P. Balkrishan, B.J. Lee, D.H. Oh, *et al*. Enhanced Oral bioavailability of Dexibuprofen by a novel solid self emulsifying drug delivery system (SEDDS). Eur. J. Pharm. Biopharm., 2009, 72: 539-545.
[65] N. Passerini, B. Albertini, B. Perissutti, *et al*.Evaluation of melt granulation and ultrasonic Spray congealing techniques to enhance dissolution of praziquantel. Int. J. Pharm., 2006, 318: 92-102.
[66] C. Cavallari, L. Rodriquez, B. Albertini, *et al*. Thermal and Fractal analysis of diclofenac/Gelucire 50/13 micro particles obtained by ultrasound-assisted atomization. J. Pharm. Sci., 2005, 94:1124-1134.
[67] E. Mehuys, J. P. Remon, A. Korst, *et al*. Human bioavailability of propranolol from a matrix-in-cylinder system with HPMC – Gelucire R Core. J Control Rel., 2005, 107: 523-536.
[68] A. Abdalla, K. Mader. Preparation and characterization of self-emulsifying pellet formation. Eur. J. Pharm. Biopharm., 2007, 66: 220-226.
[69] T. Iosio, D. Voinovich, M. Grassi, *et al*. Bilayered self-emulsifying pellets prepared by co-extrusion and spheronization: Influence of formulation variables and preliminary study on *in-vivo* absorption. Eur. J. Pharm. Biopharm., 2008, 69: 686–697.
[70] A. Seo, P. Holm, H.G. Kristensen. The preparation of agglomerates containing solid dispersions of diazepam by melt agglomeration in high shear mixer. Int. J. Pharm., 2003, 259: 161-171.
[71] N. Yukse**, A.** Karatas, Y. Ozkan, *et al*. Enhanced bioavailability of piroxicam using Gelucire 44/14 and Labrasol: *in vitro* and *in vivo* evaluation. Eur. J. Pharm. Biopharm., 2003, 56: 453-459.
[72] C. Sander, P. Holm. Porous magnesium aluminometasilicate tablets as carrier of a cyclosporine self-emulsifying formulation. AAPS Pharm. Sci. Tech., 2009, 10: 1388-1395.
[73] C. Thies, I. Santos, J. Richard. A Supercritical fluid-based coating technology 1: Process Considerations. J. Microencapsul., 2003, 20: 87-96.
[74] I. Santos, C. Thies, J. Richard. A Supercritical fluid bases coating technology 2: solubility considerations. J. Microencapsul., 2003, 20: 97-109.
[75] S. Sethia, E. Squilliante. Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional solvent evaporation method. J. Pharm. Sci., 2002, 91: 1948-1957.
[76] S. Sethia, E. Squilliante. Solid dispersion of carbamazepine in PVP K 30 by conventional solvent evaporation and supercritical methods. Int. J. Pharm., 2004, 272: 1-10.
[77] S. Sethia, E. Squilliante. *In vitro-in vivo* evaluation of supercritical processed solid dispersions: permeability and viability assessment in caco-2 cells. J. Pharm. Sci., 2004, 93: 2985-2993.
[78] L. Hu, X. Tang, F. Cui. Solid Lipid nanoparticles (SLNs) to improve oral bioavailability of poorly soluble drugs. J. Pharm. Pharmacol., 2004, 56: 1527-1535.
[79] Y. Wang, Y. Deng, S. Mao. Characterization and body distribution of beta-elemene solid lipid nanoparticles (SLN). Drug Dev. Ind. Pharm., 2005, 31: 769-778.
[80] C. Puglia, M. Ricici, F. Bonina, *et al*. Evaluation of indomethacin percutaneous absorption from nanostructured lipid carriers (NLC): *In vitro and in vivo* studies. J. Pharm. Sci., 2005, 94: 1149-1159.
[81] V. Teeranachaideekul, E. B. Souto, V.B. Junyaprasert, *et al*. Cetyl palmitate-based NLC for topical delivery of Coenzyme Q_{10}-development, physicochemical characterization and *in vitro* release studies. Eur. J. Pharm. Biopharm., 2007, 67: 141-148.
[82] K. Manjunath, V. Venkateshwarlu. Pharmacokinetics, tissue distribution and bioavailability of clozapine solid lipid nano particles after intravenous and intraduodenal administration. J. Control Rel., 2005, 107: 215-228.
[83] S. Shafiq, F. Shakeel, S. Talegaonkar, *et al*. Development and bioavailability assessment of ramipril nanoemulsion formulation. Eur. J. Pharm. Biopharm., 2007, 66: 227-243.
[84] B. Singh, L. Khurana, R. Kapil, *et al*. Development of optimized self nano emulsifying drug delivery systems of carvedilol with enhanced bioavailability potential. Drug Del., 2011, 18:599-612.
[85] P. Patil, V. Patil, A. Paradkar. Formulation of SEDDS for oral delivery of Simvastatin: *In vitro and in vivo* evaluation .Acta pharma, 2007, 57:111-122.
[86] E. Atef, A. Belmonte. Formulation and *in vitro & in vivo* characterization of phenytoin SEDDS. Eur. J. Pharm. Sci., 2008, 35: 257-263.
[87] M. Cirri, P. Mura, P.C. Mora. Liquid spray formulations of xibornol by using self-micro emulsifying drug delivery systems. Int. J. Pharm., 2007, 340: 84-91.
[88] Y. G. Bachhav, V. B. Patravale. SMEDDS of glyburide: formulation, *in vitro* evaluation, and stability studies. AAPS Pharm. Sci. Tech., 2009, 10: 482-487.
[89] S. Shafiq-un-Nabi, F. Shakeel, S. Talegaonkar, *et al*. Formulation Development and Optimization using nanoemulsion technique: A Technical Note. AAPS Pharm. Sci. Tech., 2007, 8: E1-E6.
[90] A. K. Gupta, D. K. Mishra, S.C. Mahajan. Preparation and *in vitro* evaluation of SEDDS of anti hypertensive drug valsartan. Int. J. Pharm. life Sci., 2011, 2: 633-639.
[91] D. Patel, K. K. Sawant. Oral bioavailability enhancement of acyclovir by self micro emulsifying drug delivery systems (SMEDDS). Drug Dev. Ind. Pharm., 2007, 33: 1318-1326.
[92] A. A. Date, M. S. Nagarsenker. Design and evaluation of self nanoemulsifying drug delivery systems (SNEDDS) for cefpodoxime proxetil. Int. J. Pharm., 2007, 329: 166-172.
[93] T. Gershanik, S. Benita. Positively charged self-emulsifying oil formulation for improving oral bioavailability of progesterone. Pharm. Dev. Tech., 1996, 1: 147-157.
[94] V. Borhade, H. Nair, D. Hegde. Design and evaluation of self micro emulsifying drug delivery system (SMEDDS) of tacrolimus. AAPS Pharm. Sci. Tech., 2008, 9: 13-21.
[95] B. Singh, S. Bandyopadhyay, R. Kapil, *et al*. Self Emulsifying Drug Delivery System: Formulation, Development, Characterization and Applications. Critical Review in Therapeutic Drug Carrier Systems, 2009, 26: 427–521.

[96] B. Levet-Trafit, M. S. Gruyer, M. Marjanovic, *et al*. Estimation of oral drug absorption in man based on intestine permeability in rats. Life Sci., 1996, 58: PL359-363.
[97] P. Sharma, M.V. Varma, H. P. Chawla, *et al*. In situ and *in vivo* efficacy of peroral absorption enhancers in rats and correlation to *in vitro* mechanistic studies. Farmaco, 2005, 60: 874-883.
[98] J. Yao, Y. Lu, J. P. Zhou. Preparation of nobiletin in self-micro emulsifying systems and its intestinal permeability in rats. J. Pharm. Pharm. Sci., 2008, 11: 22-29.
[99] L. Barthe, J. F. Woodley, S. Kenworthy, *et al*. An improved everted gut sac as a simple and accurate technique to measure paracellular transport across the small intestine. Eur. J. Drug Metab. Pharmacokinet., 1998, 23: 313-323.
[100] P. S. Leppert, J. A. Fix. Use of everted intestinal rings for *in vitro* examination of oral absorption potential. J. Pharm. Sci., 1994, 83: 976-981.
[101] Z. T. Chowhan, A. A. Amaro. Everted rat intestinal sacs as an *in vitro* model for assessing absorptivity of new drugs. J. Pharm. Sci., 1977, 66: 1249-1253.
[102] S. M. Khoo, A. J. Humberstone, C. J. H. Porter, *et al*. Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of halofantrine. Int. J. Pharm., 1998, 167: 155-164.
[103] Y. Ito, T. Kusawake, M. Ishida, *et al*. Oral solid gentamicin preparation using emulsifier and adsorbent. J. Control Rel., 2005, 105: 23-31.
[104] P. R. Patil, S. Praveen, R. H. Shobha Rani *et al*. Bioavailability assessment of ketoprofen incorporated in gelled self-emulsifying formulation: a technical note. AAPS Pharm. Sci. Tech., 2005, 6: E9-E13.
[105] Y. Chen, G. Li, J. G. Huang, *et al*. Comparison of self-micro emulsifying drug delivery system versus solid dispersion technology used in the improvement of dissolution rate and bioavailability of vinpocetine. Yao Xue Xue Bao, 2009, 44: 658-666.
[106] E. Taha, D. Ghorab, A. A. Zaghloul. Bioavailability assessment of vitamin A self-nanoemulsified drug delivery systems in rats: a comparative study. Med. Princ. Pract., 2007, 16: 355-359.
[107] A. K. Singh, A. Chaurasiya, A. Awasthi, *et al*. Oral bioavailability enhancement of Exemestane from Self micro emulsifying drug delivery system (SMEDDS). AAPS Pharm. Sci. Tech., 2009, 10:906-916.
[108] A. Hasegawa, M. Taguchi, R. Suzuki, *et al*. Super saturation mechanism of drugs from solid dispersions with enteric coating agents. Chem. Pharm. Bull., 1988, 36: 4941-4950.
[109] N. Leveque, S. L. Raghavan, M. E. Lane, *et al*. Use of a molecular form technique for the penetration of supersaturated solutions of salicylic acid across silicone membranes and human skin *in vitro*. Int. J. Pharm., 2006, 318: 49-54.
[110] Y. Chen, C. Chen, J. Zheng, *et al*. Development of a solid S-SEDDS of docetaxel with improved dissolution & bioavailability. Biol. Pharm. Bull., 2011, 34: 278-286.
[111] P. Gao, M. E. Guyton, T. Huang, *et al*. Enhanced oral bioavailability of poorly Water Soluble drug PNU -91325 by Supersaturable formulations. Drug Dev. Ind. Pharm., 2004, 30: 221-229.
[112] N. H. Shah, M. T. Carvajal, C. I. Patel, *et al*. Self-emulsifying drug delivery systems (SEDDS) with Polyglycolyzed glycerides for improving *in vitro* dissolution and oral absorption of lipophillic drugs. Int. J. Pharm., 1994, 106: 15-23.
[113] J. S. Woo, H. J. Suh. Oral micro-emulsion composition of Silybin. *WO patent No. 0101961*
[114] J. Kleijnen, P. Knipschild. Ginkgo biloba for cerebral insufficiency. Br. J. Clin. Pharm., 1992, 34: 352-358.
[115] J. L. Tang, J. Sun, Z. G. He. Self Emulsifying Drug Delivery System: Strategy for Improving Oral delivery of poorly soluble drugs. Current Drug Therapy, 2007, 2: 85-93.
[116] B. Shao, J. Tanq, Y. JiH, *et al*. Enhanced oral bioavailability of Wurenchun by SEDDS. Drug Dev. Ind. Pharm., 2010, 36: 1356-1363.