

NOVEL SELF-EMULSIFYING DRUG DELIVERY SYSTEM- AN APPROACH TO ENHANCE BIOAVAILABILITY OF POORLY WATER SOLUBLE DRUGS

R. Sunitha^{1*}, D. Satya Sireesha¹ and M.V. L. Aparna²

¹Hindu College of pharmacy, Guntur, Andhra Pradesh, India.

²Aditya Institute of Pharmaceutical Sciences and Research, Surampalem, Andhra Pradesh, India.

*Corresponding Author: raminenisunitha@gmail.com

ABSTRACT

Around 40% of novel chemical entities show evidence of poor aqueous solubility due to their low bioavailability. Self-emulsifying drug delivery systems (SEDDS) have gain exposure to improve the bioavailability of hydrophobic drugs. SEDDSs are belongs to lipid formulations, and size range is from 100nm (SEDDs) to less than 50nm (SMEDDs) and contains a isotropic mixtures of oils, surfactants, and co-surfactants, which are emulsified in aqueous media under conditions of gentle stirring. The theory behind dissolution rate improvement by means of SEDDS is the spontaneous development of the emulsion in the gastrointestinal tract with mild agitation provided by gastric mobility, which presents the drug in solubilized form, and the small size of the formed droplet provides a large interfacial surface area for drug absorption. Due to its small globule size, the micro/nanoemulsified drug can easily be absorbed through lymphatic pathways, thereby bypassing the hepatic first-pass effect.

INTRODUCTION

The oral route is the favorite route for chronic drug therapy, majority of drugs are frequently administered through oral route, but approximately 40% of new drug candidates have poor-water solubility and the oral delivery of such drugs is complicated for the reason that of their low bioavailability, high intra- and inter-subject variability, and not have dose linearity. To overcome these problems, a variety of strategies have been developed including the use of surfactants, lipids, permeation enhancers, micronization, salt formation, cyclodextrins, nanoparticles and solid dispersions, and self emulsifying drug delivery system, etc¹.

Recently, due to better and consistent results, there is a enormous prominence on self-emulsifying drug delivery systems

(SEDDS) to improve the oral bioavailability of lipophilic drugs. There has been emergent attention in the use of lipid excipients in self-emulsifying lipid formulations (SELFs) for the reason that of their capability to solubilize poorly water-soluble 'lipophilic' drugs and prevail over the problem of poor drug absorption and bioavailability².



There are two types of SELF systems will be present:

-Self-emulsifying drug delivery systems (SEDDS).

-Self-micro-emulsifying drug delivery systems (SMEDDS).

Both SEDDSs and SMEDDSs have different characteristics associated with improved drug release properties.

-SEDDS formulations will be having the simple binary systems which include lipophilic phase and drug, or lipophilic phase, surfactant and drug. And they are having the

droplet size in the range of 200nm-300nm and the dispersion has a turbid appearance³. And also the concentration of oil is 40-80% in SEDDS.

-The formulation of a SMEDDS requires the use of a co-surfactant to make a microemulsion. And they are characterized by having droplet size below 50nm, and the dispersion has an optically clear-to-translucent appearance. And the concentration of oil in SMEDDS is less than 20 %.

Formulation type	Composition	Characteristics
Type I	Oils without surfactants	Non-dispersing, poor solvent capacity except for highly lipophilic drugs, requires digestion to release drug
Type II	Oils and water-insoluble surfactants	SEDDS, turbid o/w dispersion (particle size 0.25-2 μm), unlikely to lose solvent capacity on dispersion, possible loss of solvent capacity on digestion
Type III	Oils, water-soluble surfactants and co-solvents	SEDDS/SMEDDS, slightly bluish to clear dispersion, possible loss of solvent capacity on dispersion, less easily digested, possible loss of solvent capacity on digestion
Type IV	water-soluble surfactants and co-solvents (oil free)	Forms a clear micellar solution on dispersion, likely loss of solvent capacity on dispersion, unlikely to be digested

Generally Conventional SEDDS are generally prepared in a liquid form. They may create a number of disadvantages like high production costs, low stability and portability, unalterable drugs or excipients precipitation may also be problematic. So to avoid these disadvantages, an alternative approach Solid-Self emulsifying drug delivery system was developed. S-SEDDS are prepared by solidification of liquid/semisolid self emulsifying (SE) ingredients into powders. They may have the combined advantages of SEDDS (i.e.enhanced solubility and bioavailability) and solid dosage forms (e.g. low production cost, convenience of process control, high stability and reproducibility, better patient compliance⁴.

Advantages of self-emulsifying drug delivery systems over conventional drug delivery systems^{5,6,7}

1. Emulsions are sensitive and metastable dispersed forms, where as S(M)EDDS are physically stable formulations that are easy to manufacture

2. Fine oil droplets of these SEDDS would pass rapidly and encourage extensive distribution of the drug all the way through the GI tract, thereby minimizing the irritation frequently encountered during extended contact between bulk drug substance and the gut wall.
3. While compare with oily solutions, these SEDDS are afford a large interfacial area for partitioning of the drug between oil and water.
4. Probable advantages of these systems include improved oral bioavailability, more consistent temporal profiles of drug absorption, selective drug targeting toward a specific absorption window in the GI tract, and drug protection from the hostile environment in the gut, protection of sensitive drugs.
5. Consequently, for lipophilic drug compounds that exhibit dissolution rate limited absorption, these systems may offer an improvement in the rate

and extent of absorption and result in more reproducible blood time profiles.

Composition of SEDDS^{7,8,9}

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.

Oils

Oils are the most important excipients in the SEDDS formulation, because they may be able to solubilize the lipophilic drug in definite quantity, and facilitate self-emulsification. By this, the amount of lipophilic drug transport can be increased via the intestinal lymphatic system, therefore absorption from the GI tract also increased by basing on the nature of triglyceride oils. In the formulation of SEDDS we have to use both long-chain triglyceride and medium-chain triglyceride oils with different degrees of diffusion. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs, due to their excellent emulsification systems, and better drug solubility properties. At present Novel semi-synthetic medium-chain triglyceride oils have surfactant properties and are widely used instead of the regular medium-chain triglyceride. Deckelbaum (1990) showing that MCT is more soluble and have a higher mobility in the lipid/water interfaces than LCT allied with a more rapid hydrolysis of MCT. In general, while using LCT, a higher concentration of cremophor RH40 was required to form microemulsions compared with MCT.

Surfactant

Numerous compounds exhibiting surfactant properties might be working for the design of self-emulsifying systems, but the choice is limited at the same time as very few surfactants are orally suitable, because Safety is a major determining factor in choosing a surfactant. Emulsifiers of natural origin are preferred since they are considered to be safer than the synthetic surfactant. The most extensively suggested ones being the non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The strength of surfactant usually ranges

between 30-60%w/w of the formulation for the formation of stable SEDDS. Surfactants contain high HLB and hydrophilicity, which assists the instantaneous formation of o/w droplets and fast dispersion of the formulation in the aqueous media. Amphiphilic surfactants can solubilize the high amounts of hydrophobic drug compounds. This can be able to prevent precipitation of the drug inside the GI lumen and for protracted continuation of drug molecules.

3. Cosurfactant/Cosolvents

Cosurfactant/Cosolvents like Spans, capryol90, lauroglycol, diethylene glycol, monoethyl ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydrofurfuryl alcohol polyethylene glycol ether (Glycofurol), etc., might help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the cosurfactants in the microemulsion systems.

Formulation of SEDDSs

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 SEDDS¹¹:

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 mix of oil, surfactant and cosolvent.
4. 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,

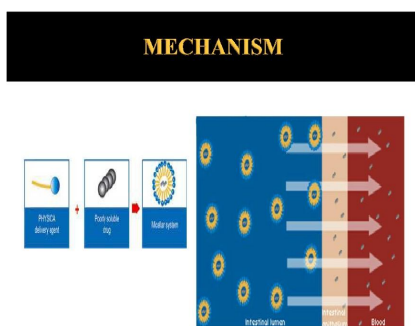
formulation is made by adding the polymer or gelling agent.

Mechanism of self-emulsification

According to Reiss, the energy required to increase the surface area of the dispersion for self-emulsification process bear less importance when compared to the entropy change that favors dispersion. Self emulsifying process is related to the free energy¹². That is free energy of the conventional emulsion is a direct function of the energy essential to create a new surface between the oil and water phases and can be described by the equation:

$$DG = S N_i p r_i 2s$$

Where, DG is the free energy related to the process, N is the number of droplets of radius r and s represents the interfacial energy. The emulsion is stabilized by emulsifying agents only after the two phases of emulsion is separated with respect to time to reduce the interfacial area. The emulsifying agent forms a monolayer of emulsion droplets, and hence reduces the interfacial energy, and providing a barrier to avoid coalescence. In the case of self-emulsifying systems, the free energy required to form the emulsion is either very low and positive, or negative. Emulsification requires very little input energy involves destabilization through contraction of local interfacial regions¹³.



Characterization of Self-Emulsifying Drug Delivery Systems

The efficiency of self-emulsification could be estimated by visual assessment, turbidity

measurements, droplet-size distribution and rate of emulsification,

Visual assessment

This may offer vital information regarding the self-emulsifying and microemulsifying property of the mixture and the resulting dispersion.

Turbidity measurement

This may recognize a capable self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

Droplet size

This is a critical factor in self-emulsification process, since it determines the rate and extent of drug release as well as the stability of the emulsion.– Photon correlation spectroscopy, microscopic techniques or a Coulter Nanosizer are mainly used for the determination of the emulsion droplet size. The reduction in droplet size to the values below 50µm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions.

Zeta potential measurement

This is used to identify the charge of the droplets. In conventional SEDDSs, the charge on an oil droplet is negative due to the presence of free fatty acids.

Determination of emulsification time

Self-emulsification time, dispersibility, appearance and flow ability were observed and scored according to techniques described in H. Shen et al. Used for the grading of formulations.

Cryo- Transmission Electron Microscopy (TEM) studies

For these studies, samples were prepared in a controlled environment confirmation system. In this study we have to get thin liquid film on the grid, by placing small amount of sample on a carbon paper, which is supported by a filter paper. Thereafter this grid is quenched in liquid ethane at -180°C and transferred to liquid nitrogen at -196°C. Then the samples were characterized with a TEM microscope.

Liquefaction time

This test is intended to estimate the time required to melt solid SEDDS in in-vivo

studies in the absence of agitation to replicated GI conditions. In this study one dosage form for example tablet is enclosed in a transparent polyethylene film and tied to the bulb of a thermometer with a thread. And then which placed in a round bottom flask containing 250 ml of simulated gastric fluid without pepsin maintained at $37 \pm 180^{\circ}\text{C}$. The time taken for liquefaction is subsequently noted.

Electron microscopic studies

Freeze-fracture electron microscopy has been used to study surface characteristics of such dispersed systems. Particle size analysis and low-frequency dielectric spectroscopy have been used to examine the self-emulsifying properties of a mixture of mono- and diglycerides of capric and caprylic acids, and Tween 80 systems.

Small-angle neutron scattering

Small-angle neutron scattering can be used to obtain information on the size and shape of the droplets. This study uses the interference effect of wavelengths scattered from different materials in a sample (different scattering-length densities).

Small-angle X-ray scattering

This small-angle scattering technique gives the information about shape and size of macromolecules, characteristic distances of partially ordered materials, pore sizes and other data. By this technique we get structural information of macromolecules between 5 and 25 nm, of repeat distances in partially ordered systems of up to 150 nm.

In addition to these techniques, others – such as nuclear magnetic resonance and differential scanning calorimetry – have also been exploited to characterize these self-emulsifying systems for an enhanced approach.

EVALUATION^{1,14}

Thermodynamic stability studies

The physical stability of a lipid based formulation is furthermore essential to its performance, which can be inauspiciously affected by precipitation of the drug in the excipient matrix. In addition, the formulation having poor physical stability can affect the formulation performance, and visual appearance is not satisfactory, and it also leads to phase separation of the excipient.

1. Heating cooling cycle

There are six cycles between the temperatures 40°C and 450°C . In between these temperatures the formulation to be stored and storage at each temperature is not less than 48 h is studied. The formulations, which are stable here, are then subjected to centrifugation test.

2. Centrifugation

Those formulations are stable above are centrifuged thaw cycles between 210°C and $+250^{\circ}\text{C}$. And the storage time at each temperature is not less than 48 h, and is carryout at 3500rpm for 30 min. If formulations that are stable here, that means they do not show any phase separation, then they are transferred for the freeze thaw stress test.

3. Freeze thaw test

Three freeze for the formulations. Those formulations passed this test showed good stability with no phase separation, creaming, or cracking.

Dispersibility test

The effectiveness of self-emulsification of oral nano or micro emulsion is assessed by using a standard USP XXII dissolution apparatus 2. One milliliter of each formulation was added to 500 mL of water at $37 \pm 0.5^{\circ}\text{C}$, at 50rpm. The in vitro performances of the formulations are visually assessed by using the following grading system:

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

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

Grade C: Fine milky emulsions that were formed within 2 min.

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

Grade E: Formulation, exhibiting either poor or minimal emulsification with large oil globules present on the surface.

Turbidimetric Evaluation

Nepheloturbidimetric evaluation is made to observe the growth of emulsification. Fixed amount of Self emulsifying system is added to suitable medium (0.1N hydrochloric acid) 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)¹⁵.

Viscosity Determination

The SEDD system is generally administered in soft gelatin or hard gelatin 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 viscosities then it are w/o type of the system.

Droplet Size Analysis Particle Size Measurements

The photon correlation spectroscopy technique was used to measure the droplet size of the emulsions. In which the light scattering was monitored at 25° c at a 90° angle, after external standardization with spherical polystyrene beads. It analyses the fluctuations in light scattering due to Brownian motion of the particles. This was done by using a Zetasizer which measures the sizes between range of 10 and 5000 nm.

Refractive Index and Percent Transmittance

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

Approaches of Self-Emulsifying Drug Delivery System

Super saturable self-emulsifying drug delivery system

Mainly the Supersaturable SEDDS (S-SEDDS) formulations have been designed and developed to reduce the surfactant effects,

since high surfactant concentration here in SEDDS formulations can direct to GI side effects, and thereby this approach can provides a better toxicity/safety profile. A new class of supersaturable formulations, including the S-SEDDS approach is designed to make an extended supersaturated solution of the drug while the formulation is released from a suitable dosage form into an aqueous medium. Supersaturation is intentional to increase the thermodynamic action of the drug further than its solubility limit, and consequently, the effect in an increased driving force for transit into and across the biological barrier, e.g., an S-SEDDS of paclitaxel (PTX) was developed using hydroxypropyl methyl cellulose (HPMC) as a precipitation inhibitor with a conventional SEDDS formulation, and a poorly soluble drug, PNU-91325, was formulated as an S-SEDDS¹⁵.

Solid self-emulsifying drug delivery system

Solid self-emulsifying drug delivery system is initially developed due to problems encountered in conventional SEDDS, that is SEDDS are normally prepared as liquid dosage forms that can be administered in soft gelatin capsules, which have some disadvantages particularly in the manufacturing process. An alternative method is the inclusion 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/spheronization to provide a good *in vitro* drug release (100% within 30 minutes, T50% at 13 minutes)^{16,17}.

Technique of Solid Self-Emulsifying Drug Delivery System Development

Solid SEDDS were mainly developed by adsorption of solid carriers, spray drying, melt extrusion, dry emulsion, solid dispersion, etc. These solid SEDDS can be converted into pellets, tablets and capsules.

Solid carriers

The advantage of solid carriers is, they have the property to take up liquid/semisolid formulation as self emulsifying system (SES). The procedure involves the incorporation of

SES into free-flowing powder materials which has adsorption capacity and mixes them uniformly using a blender. This mixture is solidified to powder forms using three kinds of adsorbents: microporous calcium silicate (Florite™ RE), magnesium aluminum silicate (Neusilin™ US2) and silicon dioxide (Sylysia™ 320). After then this powder mixture is filled into capsule or added to more ingredients before compression into tablets.

Spray drying

In this technique, the formulation (which contains oil, surfactant, drug, solid carrier, etc.,) is sprayed into a drying chamber through a nozzle. The volatile vehicles are evaporated and leaving the small solid particles. These particles are then filled into capsules or compressed into tablets.

Melt extrusion

This formulation technique depends on the property of the plastic mass material which can be easily extruded with pressure. Here, the powder agglomeration is achieved through the addition of a binder that melts at low temperature. It is a one-step process, there is no need for addition of liquid form of excipient but a constant temperature and pressure needs to be maintained¹².

Dry emulsion

It is mainly o/w emulsion, which is then converted into solid form by spray drying/solid carrier/freeze drying.

Dosage Forms From Self-Emulsifying System:

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.

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^{17,35}.

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 ester²⁰.

Self-emulsifying sustained/controlled-release pellets

Serratori et al. prepared SE controlled-release pellets 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/spheronization and contained two water-insoluble model drugs (methyl and propyl parabens); SES contained mono-glycerides and Polysorbate 80^{16,22}.

Self-emulsifying nanoparticles

For the production of self emulsifying nanoparticles, nanoparticle technology might be used successfully. Under these one of the technique 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 nanoparticle 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 selfnanoemulsifying 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).

Self-emulsifying beads

SES can be formulated as a solid dosage form by using less solidifying excipient. Patil and Paradkar 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 PPB²⁴.

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 adsorbent³⁶.

Selfemulsifying sustained release microspheres

Zedoary turmeric oil (ZTO; a traditional Chinese medicine) shows effective pharmacological actions like tumor suppressive, antibacterial, and antithrombotic activity. You et al. prepared solid SE sustained release microspheres using the quasi-emulsion-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 SEDDS²⁸.

Self-emulsifying implants

SE 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-co-glycolide)(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 SES³⁸.

Applications of sedds^{31,32,34,36}

DRUG	SURFACTANT	OIL	COSOLVENT	RESULT
Ketoprofen	Captex 200	Tween 80	Capmul MCM	Increased bioavailability
Atorvastatin	Labrafil, estol and isopropyl myristate	Cremophor EL, Cremophor RH40	Labrafil 1944	Oral bioavailability increases 1.55 times than conventional tablets
Carvedilol	Labrasol	Labrafil M 1944 CS	Transcutol P	Bioavailability increased upto 413%
Simvastatin	Caproyl 90	Cremophor EL	Carbitol	Oral bioavailability is 1.5 times higher than conventional tablets
Itraconazole	Tocopherol acetate	Pluronic L64	Transcutol	Oral bioavailability increased without influence of food
Coenzyme Q ₁₀	Captex 200	Labrasol	Lauroglycerol	Oral bioavailability increased upto 2 folds than powder formulation
Diclofenac sodium (SE Tablet)	Goat fat	Tween 65	-----	Better release rate

Examples of some marketed products in which it has been used^{3,34,46}

1. Targretin soft gelatin capsule
2. Gengraf hard gelatin capsule
3. Ritonavir soft gelatin capsule
4. Ritonavir oral solution
5. Sandimmune soft gelatin capsules
6. Sandimmune oral solution
7. Agenerage Soft gelatin capsule
8. Agenerage oral solution
9. Nerol soft gelatin Capsule
10. Nerol Oral Solution
11. Lamprene soft gelatin capsule
12. Fortavase soft gelatin capsule
13. Rocaltrol soft gelatin capsule,
14. Hectrol soft gelatin capsule
15. Rocatrol oral solution
16. Avodat soft gelatin capsule
17. Depakene capsule
18. Norvir soft gelatin capsule
19. Marinol soft gelatin capsule
20. Accutane soft gelatin capsule
21. Vesanoid soft gelatin capsule
22. Accutane soft gelatin capsule
23. Vesanoid soft gelatin capsule
24. Accutane soft gelatin capsule
25. Prometrium soft gelatin capsule
26. Vesanoid soft gelatin capsule

CONCLUSION

Self-emulsifying drug delivery systems are a hopeful approach for the formulation of lipophilic drugs. Several studies have been confirmed that SEDDS provides significantly improved solubility/dissolution, absorption and bioavailability of hydrophobic drugs. As improvements or alternatives of conventional liquid SEDDS, S-SEDDS are superior in

reducing production cost, simplifying industrial manufacture, and improving stability as well as patient compliance. Most importantly, S-SEDDS are very convenient to develop various solid dosage forms for oral and parenteral administration. Moreover, GI irritation is avoidable and controlled/sustained release of drug is achievable. Even though it is an effective technique, here also some disadvantages are there, like lack of good predictive in vitro models for assessment of the formulations, and higher concentrations of surfactant to be used may cause some allergic reactions. Further development will be based on in vitro - in vivo correlations and therefore different prototype lipid based formulations need to be developed and tested using in vivo and in vitro methods.

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