Research Article **CODEX: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

A REVIEW: SELF EMULSIFYING DRUG DELIVERY SYSTEM

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ABSTRACT

Drugs are most often administered by the oral route. However, more than 40% of new chemical entities exhibit poor aqueous solubility, resulting in unsatisfactory oral drug delivery. Recently, much attention has been focused on selfemulsifying drug delivery systems (SEDDS) to improve the oral bioavailability of poorly aqueous soluble drugs. SEDDS are isotropic mixtures of oil, surfactants, solvents and co-solvents/surfactants. The principal characteristic of these systems is their ability to form fine oil-in-water (o/w) emulsions or microemulsions upon mild agitation following dilution by an aqueous phase. For lipophilic drugs, which display dissolution rate-limited absorption, SEDDS may be a promising strategy to improve the rate and extent of oral absorption. This article gives an over view of formulation, development, characterization, recent approaches and applications of self-emulsifying drug delivery systems.

KEYWORDS

Self-emulsifying drug delivery system (SEDDS), Surfactants and Co-solvent.

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INTRODUCTION[1-10]

Self-emulsifying drug delivery systems (SEDDSs) have gained exposure for their ability to increase solubility and bioavailability of poorly soluble drugs. SEDDSs are isotropic mixtures of oils and surfactants, sometimes containing co-solvents, and can be used for the design of formulations in order to improve the oral absorption of highly lipophilic compounds. SEDDSs emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. SEDDS can be orally administered in soft or hard

gelatine capsules and form fine, relatively stable oil-in-water emulsions upon aqueous dilution. This article presents an overview of SEDDSs and their applications.

In recent years, the formulation of poorly soluble compounds presented interesting challenges for formulation scientists in the pharmaceutical industry. Up to 40% of new chemical entities discovered by the pharmaceutical industry are poorly soluble or lipophilic compounds, which leads to poor oral bioavailability, high intra- and inter-subject variability, and lack of dose proportionality.

In the oral formulation of such compounds, a number of attempts - such as decreasing particle size, use of wetting agents, coprecipitation, and preparation of solid dispersions - have been made to modify the dissolution profile and thereby improve the absorption rate. Recently, much attention has focused on lipid-based formulations to improve the bioavailability of poorly water soluble drugs. Among many such delivery options, like incorporation of drugs in oils, surfactant dispersion, emulsions and liposomes, one of the most popular approaches are the self-emulsifying drug delivery systems (SEDDSs).

SEDDSs are mixtures of oils and surfactants, ideally isotropic and sometimes containing cosolvents, which emulsify spontaneously to produce fine oil-in-water emulsions when introduced into an aqueous phase under gentle agitation. Self-emulsifying formulations spread readily in the gastrointestinal (GI) tract, and the digestive motility of the stomach and the intestine provide the agitation necessary for selfemulsification. These systems advantageously present the drug in dissolved form and the small droplet size provides a large interfacial area for the drug absorption. SEDDSs typically produce emulsions with a droplet size between 100-300 nm while self-microemulsifying drug delivery systems (SMEDDSs) form transparent microemulsions with a droplet size of less than 50 nm. When compared with emulsions, which are sensitive and metastable dispersed forms, SEDDSs are physically stable formulations that are easy to manufacture. Thus, 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 (Table No.1).

ADVANTAGES

Potential advantages of these systems (SEDDS) include

- Enhanced oral bioavailability enabling reduction in dose.
- More consistent temporal profiles of drug absorption.
- Selective targeting of drug(s) toward specific absorption window in GIT.
- Protection of drug(s) from the hostile environment in gut.
- Control of delivery profiles.
- Reduced variability including food effects.
- Protection of sensitive drug substances.
- High drug payloads.
- Liquid or solid dosage forms.

These formulations have attracted interest because they can improve the bioavailability of compounds that fall into Class II of the biopharmaceutical classification system (BCS). Class II compounds are poorly water soluble and highly permeable. This bioavailability enhancing property has been associated with a number of *in vivo* properties of lipidic formulation including:

1. The formation of fine dispersions and micellar suspensions to prevent precipitation and recrystallization of the drug compound.
2. The ability of certain lipid compounds and their metabolites to initiate changes in the gastrointestinal fluid to favour improved drug absorption.
3. The inhibition of cellular efflux mechanisms, which keep drugs out of the circulation.
4. Certain lipidic excipients are associated with selective drug uptake into the lymphatic transport system, thereby reducing the effect of first-pass drug metabolism in the liver.

DISADVANTAGES OF SEDDs

- Traditional dissolution methods do not work, because these formulations potentially are

dependent on digestion prior to release of the drug.

- This *in vitro* model needs further development and validation before its strength can be evaluated.
- Further development will be based on *in vitro* - *in vivo* correlations and therefore different prototype lipid based formulations needs to be developed and tested *in vivo* in a suitable animal model.
- The drawbacks of this system include chemical instabilities of drugs and high surfactant concentrations in formulations (approximately 30-60%) which GIT.

COMPOSITION OF SEDDSs

The self-emulsifying process is depends on:

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

Oils

Oils can solubilize the lipophilic drug in a specific amount. It is the most important excipient because it can facilitate self-emulsification and increase the fraction of lipophilic drug transported via the intestinal lymphatic system, thereby increasing absorption from the GI tract. Long-chain triglyceride and medium-chain triglyceride oils with different degrees of saturation have been used in the design of SEDDSs. Modified or hydrolyzed vegetable oils have contributed widely to the success of SEDDSs owing to their formulation and physiological advantages. Novel semisynthetic medium-chain triglyceride oils have surfactant properties and are widely replacing the regular medium- chain triglyceride.

Surfactant

Nonionic surfactants with high hydrophilic-lipophilic balance (HLB) values are used in formulation of SEDDSs (e.g., Tween, Labrasol, Labrafac CM 10, Cremophore, etc.). The usual surfactant strength ranges between 30-60% w/w of the formulation in order to form a stable SEDDS. Surfactants have a high HLB and hydrophilicity, which assists the immediate formation of o/w droplets and/or rapid spreading of the formulation in the aqueous media. Surfactants are amphiphilic in nature and they can dissolve or solubilize relatively high amounts of hydrophobic drug compounds. This can prevent precipitation of the drug within the GI lumen and for prolonged existence of drug molecules.

Co-solvents

Co-solvents like diehylene glycol monoethyle ether (transcutol), propylene glycol, polyethylene glycol, polyoxyethylene, propylene carbonate, tetrahydro-furfuryl alcohol polyethylene glycol ether (Glycofurol), etc., may help to dissolve large amounts of hydrophilic surfactants or the hydrophobic drug in the lipid base. These solvents sometimes play the role of the cosurfactant 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 SEDDS:

- The solubility of the drug in different oil, surfactants and cosolvents.
- The selection of oil, surfactant and cosolvent based on the solubility of the drug and the preparation of the phase diagram.
- The preparation of SEDDS formulation by dissolving the drug in a mix of oil, surfactant and cosolvent.

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, self-emulsification occurs when the entropy change that favors dispersion is greater than the energy required to increase the surface area of the dispersion. The free energy of the conventional emulsion is a direct function of the energy required 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 associated with the process (ignoring the free energy of mixing).

N - is the number of droplets of radius r and

s - represents the interfacial energy.

The two phases of emulsion tend to separate with time to reduce the interfacial area, and subsequently, the emulsion is stabilized by emulsifying agents, which form a monolayer of emulsion droplets, and hence reduces the interfacial energy, as well as providing a barrier to prevent coalescence.

TECHNIQUE OF SOLID SELF-EMULSIFYING DRUG DELIVERY SYSTEM DEVELOPMENT[11-17]

Solid SEDDS were developed mainly 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

These solid carriers have the property to absorb liquid/semisolid formulation as SES. It is a simple procedure, where SES is incorporated into a free-flowing powder material which has adsorption quality. The mixture is uniformly adsorbed by mixing in a blender. This solid mixture is filled into capsule or added to more excipient before compression into tablets. The above 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).

Spray drying

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

Melt extrusion

This formulation technique depends on the property of the plastic mass material which can be easily extruded with pressure. Here, there is no need for addition of liquid form of excipient but a constant temperature and pressure needs to be maintained.

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 tablets

Nazzal *et al*. developed self-nanoemulsified tablet dosage form of ubiquinone. The main objectives of this study were to study the effect of formulation ingredients on the release rate of ubiquinone and to evaluate an optimized self-nanoemulsified tablet formulation. The first self-nanoemulsion system containing ubiquinone was prepared as a nanoemulsion. This nanoemulsion was adsorbed by granular materials and then compressed to form tablets. The optimized formulation of coenzyme Q10 self-nanoemulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minutes.

Attama *et al*. formulated the solid SESs in the delivery of diclofenac. This solid SES was developed using goat fat and Tween. The fatty material and surfactant were heated together and melted. This was added to weighed quantity of drug and the drug was dissolved in the molten mass. This molten mass was then poured into plastic mould and cooled. These tablets liquify at body temperature without agitation, and under the gastrointestinal conditions, agitation due to peristaltic movement will

lower the liquification time, resulting in faster emulsification with increased plasma concentration. Different formulation ratios show varying dissolution profile at constant speed/agitation. These tablets showed good release profiles with acceptable tablet properties.

Self-emulsifying pellets

Tuleu *et al*. conducted comparative bioavailability study in dogs by comparing a self-emulsifying formulation of progesterone presented as pellets and in the liquid form with an aqueous suspension of progesterone. The *in vitro* dissolution tests showed that nearly 100% of progesterone dissolved within 30 minutes and within 5 minutes from capsules containing progesterone dissolved in SES. From the aqueous suspension, 50% of the dose was released within 60 minutes. They also tested pellets administered orally to dogs versus the same dose of progesterone dissolved in liquid SES in capsules or a suspension of micronized progesterone. Figure No.1 shows the processing of lipid and coadministered drug. In their study, it was found that SES pellets and SES solution had higher plasma levels of progesterone at each time point as compared to the aqueous suspension of progesterone.

Franceschinis *et al*. developed a method of producing self-emulsifying pellets (SEPs) by wet granulation. They first developed a binder solution containing an oil (mono and diglycerides), polysorbate 80 and model drug nimesulide in different proportions. This oil-surfactant mixture was stirred, then added to water to form SES. The second step was to prepare granules from microcrystalline cellulose (MCC) and lactose in a granulator. These binder solutions were sprayed onto the granules and pellets were formed by increasing the speed of the granulator. Pellets were able to generate significantly smaller droplets with respect to the corresponding emulsions. Serratoni *et al*. presented controlled drug release from SEPs.

SESs were formed by mixing oil-surfactant within solublized drug in appropriate concentrations because higher quantity of drug incorporated into SES could be precipitated when diluted with water. This SES was added into damp mass of MCC and lactose monohydrate, water was then added to the prepared wet mass for extrusion-spheronization to form pellets. These pellets were coated by hydrophilic polymers, namely ethyl cellulose, and then coated by aqueous solution of HPMC in a fluid bed coater. The ability of this formulation is to enhance dissolution of the model drug, where dissolution results for the uncoated pellets containing methyl or propyl parabens, with and without the addition of SES was compared.

Ahmed abdalla and Karsten Mader investigated preparation and characterization of SEPs formulation. They formulated three SESs separately by melting Cithrol Glecerides mono sterates (mono and diglycerides) and solutol HS. To this was added drug, dye and spin probe. Then water was added to the molten lipid blend until a creamy mass was formed, and then dry MCC was added to it to form a suitable mass for extrusion.

The dye was added for assessment of self-emulsification and spin probe was added for the release kinetics and microenvironment of pellets, during release process, which were assessed using electron spin resonance spectroscopy. The dissolution profile showed complete release of drug as diazepam from the non-self-emulsifying GMS/MCC pellets. It had a threefold duration of action. Nearly 90% of the drug was released after an hour, while only 55% was released from the GMS/MCC pellets. Pellets composed of MCC/GMS were only capable of releasing diazepam until the saturation solubility was reached.

Tosio *et al*. prepared bilayered SEPs. SEP was formed by coextrusion-speronization with two cohesive layers. In that, type 1 pellets had formulation A (a matrix made of lactose and MCC loaded with an SES dispersion) in the inner part and formulation B (an inert matrix containing lactose, MCC, and water) in the outer part, and type 2 pellets had formulation B in the inner core and formulation A externally. SEPs were formulated in two steps: first, oil-surfactant mixture was prepared and then added to water to form SES and this mixture was then loaded into MCC and lactose to form suitable extrusion-speronization mass for pellets. Pellets of

type I plus 2% of croscarmellose sodium released 90% of vinpocetine as a model drug within 30 minutes; pellets of type II were released in 20 minutes and from the physical mixture only 25% of drug was released after 60 minutes.

Self-emulsifying beads

SES can be formulated as a solid dosage form by using less excipient. Patil and Paradkar discovered that deposition of SES into microporous 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, was found to govern the loading efficiency and *in vitro* drug release from SES loaded PPB.

Self-emulsifying microsphere

You *et al*. formulated solid SE sustained release microspheres using the quasi-emulsion solvent diffusion method for the spherical crystallization technique. Zedoary turmeric oil release behavior could be controlled by the ratio of HPMC acetate succinate to Aerosil 200 in the formulation. The plasma concentration time profiles were achieved after oral administration of such microspheres to rabbits, with a bioavailability of 135.6% with respect to the conventional liquid SEDDS.

Self-emulsifying nanoparticles

Nanoparticle technology can be applied to the formulation of self-emulsifying nanoparticle. One of the solvents is an injection. In this method, the prepared molten lipid mass contains lipid, surfactant and drug. This lipid molten mass is injected dropwise into a non-solvent system. This is filtered and dried to get nanoparticles. By this method, 100 nm size particle with 70-75% drug loading efficiency is obtained. The second technique is sonication emulsion diffusion evaporation. By this method are coloaded 5-flurouracil and antisense epidermal growth factor receptor (EGFR) plasmids into biodegradablepolylactidecoglycolide (PLGA)/carbox methyl -chitosan (CMC) nanoparticles. The mixture of PLGA and CMC had an SE effect, with no additional surfactant required. Trickler *et al.* developed a novel nanoparticle drug delivery system consisting of chitosan and glycerylmonooleate (GMO) for the delivery of PTX. These chitosan/GMO nanoparticles with bioadhesive properties increased cellular association and were prepared by multiple emulsion (o/w/o) solvent evaporation methods.

CHARACTERIZATION OF SEDDSs

The primary means of self-emulsification assessment is visual evaluation. The efficiency of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

Visual assessment

This may provide important information about the self-emulsifying and microemulsifying property of the mixture and about the resulting dispersion.

Turbidity Measurement

This is to identify efficient self-emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time.

Droplet Size

This is a crucial factor in self-emulsification performance because 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 of the droplet size to values below 50 μm 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 presence of free fatty acids.

Determination of emulsification time

Self-emulsification time, dispersibility, appearance and flowability was observed and scored according to techniques described in H. Shen et al. used for the grading of formulations.

APPLICATION

SEDDS formulation is composed of lipids, surfactants, and cosolvents. The system has the

ability to form an oil-in-water emulsion when dispersed by an aqueous phase under gentle agitation. SEDDSs present drugs in a small droplet size and well-proportioned distribution, and increase the dissolution and permeability. Furthermore, because drugs can be loaded in the inner phase and delivered by lymphatic bypass share, SEDDSs protect drugs against hydrolysis by enzymes in the GI tract and reduce the presystemic clearance in the GI mucosa and hepatic first-pass metabolism. Table No.1 shows the SEDDSs prepared for oral delivery of lipophilic drugs in recent years.

SMEDDS in research or development include formulations of the drugs anethole trithione,oridonin,curcumin,vinpocetine, tacrolimus, berberine hydrochloride, nobiletin, piroxicam, anti-malaria drugs beta-Artemether and halofantrine, anti-HIV drug UC 781,nimodipine,exemestane, anti-cancer drugs 9-nitrocamptothecin (9-NC) paclitaxel, and seocalcitol, alprostadil (intraurethral use), probucol, itraconazole, fenofibrate, acyclovir, simvastatin, xibornol,silymarin, alpha-asarone, enilconazole, puerarin (an isoflavone found in Pueraria lobata) atorvastatin, heparin, carvedilol, ketoconazole, gentamicin, labrasol, flurbiprofen, celecoxib, danazol, cyclosporine, and idebenone.

Application of Self-Emulsifying Drug Delivery System

Supersaturable self-emulsifying drug delivery system

The high surfactant level typically present in SEDDS formulations can lead to GI side effects and a new class of supersaturable formulations, including supersaturable SEDDS (S-SEDDS) formulations, have been designed and developed to reduce the surfactant side effects and achieve rapid absorption of poorly soluble drugs.The S-SEDDS approach is designed to generate a protracted supersaturated solution of the drug when the formulation is released from an appropriate dosage form into an aqueous medium. Surpersaturation is intended to increase the thermodynamic activity of the drug beyond its solubility limit and, therefore, to result 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-SEDDS. It is worth emphasizing that the significantly reduced amount of surfactant used in the S-SEDDS formulation approach provides a better toxicity/safety profile than the conventional SEDDS formulations.

Solid self-emulsifying drug delivery system

SEDDS are normally prepared as liquid dosage forms that can be administrated in soft gelatine capsules, which have some disadvantages especially in the manufacturing process. An alternative method is the incorporation of liquid self-emulsifying ingredients into a powder in order to create a solid dosage form tablets, capsules. A pellet formulation of progesterone in SEDDS has been prepared by the process of extrusion/spheronization to provide a good *in vitro* drug release (100% within 30 minutes, T50% at 13 minutes).

RECENT APPROACHES IN SELF-EMULSIFYING DRUG DELIVERY SYSTEM

1. SEDDS of coenzyme Q10 was prepared and this resulted in enhanced bioavailability and reduced toxicity.
2. Lipophilic compound WIN 54954 was formulated as SEDDS in triglyceride oil/non-ionic surfactant mixtures and resulted in improved reproducibility of the plasma profile in terms of *C*max and *T*max.
3. Self-microemulsifying drug delivery system (SMEDDS) of simavastin was developed to enhance its oral bioavailability. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds.
4. A novel SEDDS of PTX (used for the treatment of solid tumors) was prepared and it was found that SEDDS was chemically stable for at least 1 year when kept as two part formulation and also the drug loading was increased by approximately fivefold. Compared to marketed i.v. formulation,

5. The excipient presented a significantly reduced cytotoxicity and led to a stable microemulsion.
6. An antimalarial drug, Halofantrine, was prepared as SEDDS and SMEDDS and resulted in an eightfold improvement in absolute oral bioavailability relative to previous data of the solid.
7. Enhanced bioavailability upto 1.88 of silymarin was achieved by SMEDDS.
8. Using SEDDS, self-nanoemulsified drug delivery system (SNEDDS) of ubiquinone was prepared and the study revealed that SNEDDS overcame the drawbacks of the traditional emulsified system, such as low solubility and irreversible precipitationof the active drug in the vehicle with time.
9. The two novel SMEDDSs containing Labrasol with different dilutions on tight junction were studied and found that Labrasol at a concentration of 0.1 and 1% was shown to increase the permeability of mannitol by 4.6-fold and 33.8-fold, respectively.
10. The solid self-emulsifying system (SES) was used in the delivery of diclofenac and results indicated that diclofenac could be comfortably administered in the form of self-emulsifying tablets using goat fat and Tween 65 admixtures.
11. SEDDS containing ketoprofen was formulated as sustained release dosage form and it was found that drug release was increased.

Table No.1: Difference between SEDDS and SMEDDS

SEDDS	SMEDDS
Can be a simple binary formulation with the drug and a lipidic excipient able to self-emulsify in contact with gastrointestinal fluids (GIF) Or A system comprising drug, surfactant, oil (also referred to as lipid phase).	Are composed of the drug compound, surfactant, co-surfactant, and oil (or lipid phase).
SEDDS and SMEDDS form a fine oil-in-water dispersion in contact with GIF	
Lipid droplet size in the dispersion ranges from 200 nm–5 µm providing a large surface area for absorption. The dispersion has a turbid appearance.	Lipid droplet size in the dispersion is < 200 nm providing a large surface area for absorption. The dispersion has an optically clear to translucent appearance.
SEDDS and SMEDDS have high solubilizing capacity high dispersibility capacity	
SEDDS systems are not thermodynamically stable in water or physiological conditions. Development/optimization of SEDDS may require the development of ternary phase diagrams.	SMEDDS systems are thermodynamically stable in water or physiological conditions. Pseudo-ternary phase diagrams are required to optimize SMEDDS.
SEDDS and SMEDDS formulations can be prepared as liquids and semi-solid for capsule dosage forms and solid forms for tabletting	

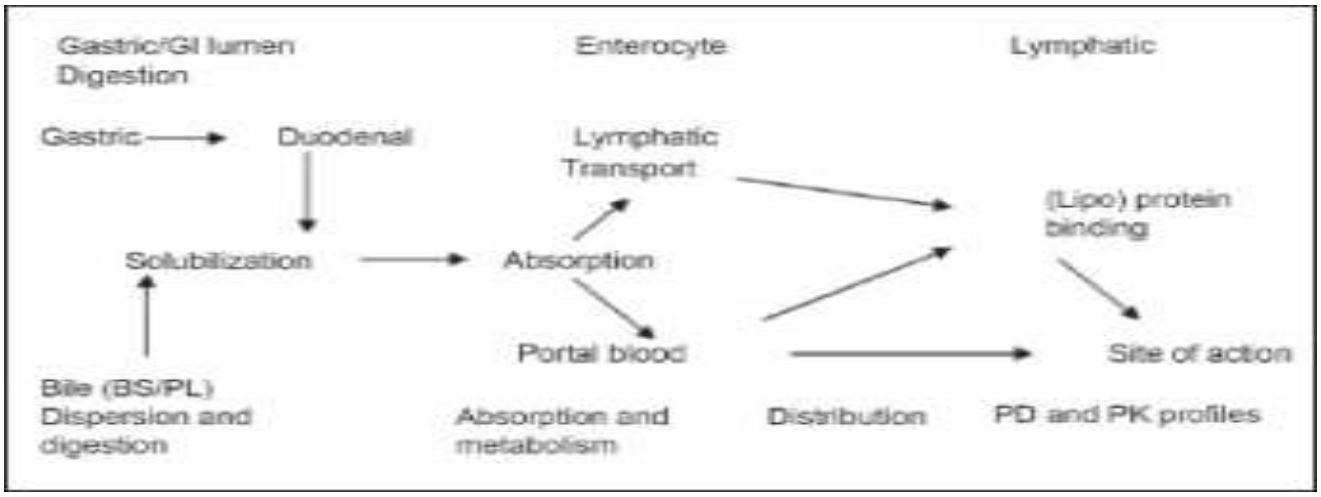

Figure No.1: Processing of lipid and co-administered drug

CONCLUSION

Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of hydrophobic drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. With future development of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs.

ACKNOWLEDGEMENT

The authors are sincerely thanks to A.M Reddy Memorial College of Pharmacy, Narasaraopet, Guntur, Andhra Pradesh, India for providing the facilities to complete this review work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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Please cite this article in press as: Ramaa Bharathi P. *et al*. A review: self-emulsifying drug delivery system, *International Journal of Research in Pharmaceutical and Nano Sciences*, 2(2), 2013, 203-212.