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SELF EMULSIFYING DRUG DELIVERY SYSTEM: AN APPROACH TO ENHANCE SOLUBILITY OF POORLY WATER SOLUBLE DRUGS

Parag Rajkumar Bondhare*[1] and A. M. Mahale[2]

[1*]Sudhakarrao Naik Institute of Pharmacy, Pusad, Yavatmal, Maharashtra, India.
[2]Department of Pharmaceutics, Sudhakarrao Naik Institute of Pharmacy, Pusad, Yavatmal, Maharashtra, India.

ABSTRACT

Oral drug delivery is convenient and most common method for delivery of drugs, because of this reason most drugs are administered via oral route. Administration of drugs orally should possess very good aqueous solubility for better absorption and bioavailability. But studies have shown that up to 35%-40% of new drugs possess poor aqueous solubility which leads to poor bioavailability. Self-emulsifying drug delivery systems are new drug delivery systems that were prepared with the purpose of enhancing solubility and bioavailability of poor aqueous soluble drugs. The unique feature of this delivery system is the ability to self-emulsify, that is, their ability to form micro emulsions or oil-in-water emulsions when diluted in the aqueous phase because of the gentle agitation of the gastrointestinal tract used for hydrophobic drugs having dissolution rate-limited absorption. The present review provides an updated information of advancements in SEDDS with regard to its composition, evaluation, different dosage forms and newer techniques to convert liquid SEDDS to solid and also various applications.

KEYWORDS

Self emulsifying drug delivery system, Solid self emulsifying drug delivery system and Bioavailability.

Author for Correspondence:

Parag Rajkumar Bondhare,

Sudhakarrao Naik Institute of Pharmacy,

Pusad, Yavatmal, Maharashtra, India.

Email: prbondhare@gmail.com

INTRODUCTION

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

to enhanced bioavailability. There are various techniques to overcome such problems arised due to low solubility and bioavailability, which result ineffective 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 improve[2].

The another name of Self-emulsifying drug delivery systems are SEDDS. They are isotropic mixtures of drug, oil, surfactants and hydrophilic solvents or co-solvents. Self-emulsifying drug delivery system can be administered orally via soft or hard gelatin capsules or tablets. When these are get dissolved in aqueous medium, by mild agitation of gastrointestinal fluids they form fine oil-in-water emulsions. This is the process of self-emulsification. The process of self-emulsification can be better explained with the ouzo effect which occurs in anise-flavoured liquors where an oil-in-water emulsion is formed when the anise comes in contact with water. These technique is used oral absorption of highly lipophilic drugs[3].

Advantages[4,5]

1. These technique gives protection to sensitive drug substance.
2. It have high drug loading efficiency.
3. Shows protection of drug from gut environment.
4. Control of delivery profile.
5. Also have high drug loading efficiency.
6. After administration gives quick Onset of Action
7. The main advantage is reduction in the Drug Dose.
8. Easy to Manufacture and Scale-up.
9. The improvement in oral bioavailability is occurred.
10. Inter-subject and Intra-subject variability and food effect.
11. Ability to deliver peptides that are prone to enzymatic hydrolysis in GIT.
12. Shows more consistent drug absorption.

Disadvantages[5,6]

1. The high content of surfactant presents in self-emulsifying drug delivery system which ranges between 30% - 60% irritates the GIT.
2. In-vitro models of self-emulsifying formulations lack good predicative studies on assessment of the formulation.
3. Co-solvents which are volatile in nature can migrate on the soft or hard gelatin capsule shell leading to the precipitation of lipophilic drug.
4. The usual dissolution evaluation tests do not work because SEDDS formulations potentially depend on digestion before the release of the drug.
5. The chemical instabilities are observed in the self-emulsifying drug delivery systems.
6. Production cost is expensive.
7. Self-emulsifying drug delivery system formulations containing a high number of components become difficult to validate.

COMPOSITION OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

1. Drug/Active Pharmaceutical Ingredient
2. Oils
3. Surfactants
4. Co-surfactants

Drug/Active Pharmaceutical Ingredient

According to Biopharmaceutical classification system, as increase the solubility, the class II drugs which have low solubility and high permeability are used in the SEDDS[7].

Oils

Oil is the most important excipient. It is responsible for facilitating the process of self-emulsification. Due to the impact of oil in SEDDS, they are also called self-emulsifying oil formulations. It helps in the solubilizing lipophilic drugs. Natural and synthetic oils are used in self-emulsifying drug delivery system. They increase the fragments of lipophilic drugs that pass through the intestinal lymphatic system; this increases the absorption from gastrointestinal tract depending on the nature of triglyceride.

Various degrees of saturation of low chain triglyceride (LCT) and Medium chain triglyceride (MCT), monoglycerides, diglycerides have been used in the formulations of SEDDS. Semi synthetic medium chain triglycerides are novel compounds. They are defined as compounds having both hydrophilic and lipophilic properties as well as having surfactant properties. Novel semi-synthetic medium chain triglycerides are amphilic compounds and they are rapidly replacing the regular MCT oils[8].

Hydrolyzed vegetable oils are widely used since they form a good emulsification system with number of approved orally administered surfactants. They also show better drug solubility properties. Edible oils are not continually used due to their poor ability to soluble large amounts of lipophilic drugs.

Improved or hydrolyzed vegetable oils have been mostly used since these excipients form rapid emulsification systems with a large number of surfactants approved for oral administration and exhibit better drug solubility properties. They offer formulative and physiological advantages and their degradation products resemble the natural end products of intestinal digestion[9].

Surfactants

Several compounds exhibiting surfactant properties may be used for the formulation of self-emulsifying systems, but the choice is limited as very less surfactants are orally acceptable. The most widely are non-ionic surfactants with a relatively high hydrophilic-lipophilic balance (HLB) and less toxicity than ionic surfactants but they may lead to reversible changes in the permeability of the intestinal lumen. Security is a vital factor in choosing a surfactant. Nonionic surfactants are mostly used because they are less toxic compared to ionic surfactants but they may alter the permeability of the intestinal lumen by reversible changes[10].

Surfactants of natural sources are usually preferred to synthetically made surfactants but the natural emulsifiers have restrained self-emulsification ability. In some cases, the increase in the surfactant concentration leads to a decrease in mean droplet size as seen in SMEEDS.

This is because of the stability of the oil droplets due to the positioning of surfactant molecule in oil-water interface. Also an increase in surfactant concentration leads to an increase in mean droplet size. This can be explained by the disruption on the interface educed by enhanced water penetrations into oil droplets by which the increased surfactant concentration acts as a medium leading to the extrusion of oil droplets into the aqueous phase.

Surfactants recruit for use in the SEDDS preparation act by various mechanisms to improve the bioavailability which include increased permeability of intestinal epithelium, reduced or inhibited p-glycoprotein drug efflux, enhanced drug dissolution and increased tight junction permeability. High quantity of surfactant can cause reversible changes in the permeability of intestinal wall. The non-ionic group of surfactants consists of tween and span[11].

Co- Surfactants

The formulation of an optimum SMEDDS requires relatively high concentrations of surfactants but it causes GI irritation. So co-surfactant is used to reduce concentration of surfactant. Use of the co-surfactant with the surfactant is to lower the interfacial tension to a very small even transient negative value. At these stage the interface would expand to form fine dispersed droplets, and subsequently adsorb more surfactant and surfactant/co-surfactant until their bulk condition is depleted enough to make interfacial tension positive again.

This process known as ‘spontaneous emulsification’ forms the micro emulsions. Organic solvents, suitable for oral administration may help to dissolve large amounts of either the hydrophilic surfactant or the drug in the lipid base and can act as co-surfactant in the self-emulsifying drug delivery systems[3].

Such systems may exhibit some advantages over the other formulations when incorporated in capsule dosage forms, since alcohol and other volatile co-solvents in the conventional self-emulsifying

formulations are known to travel into the shells of soft gelatin or hard sealed gelatin capsules result in the precipitation of the lipophilic drug. The lipophilic drug dissolution ability of the alcohol free formulation may be limited. These alcohol not containing SEDDS systems have advantages over the other formulations because in capsule dosage forms, alcohol and volatile solvents travel to the soft or hard gelatin capsule shell causing precipitation of lipophilic drug. In alcohol not containing formulation systems, lipophilic drug dissolution is limited. Proper choice should be considered in the selection of excipients[12].

Mechanism of self emulsification

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

$$\Delta G = \Sigma N \pi r2 \sigma.$$

Where, ΔG is the free energy associated with the process (ignoring the free energy of mixing), N is the number of droplets of radius, r, and σ represents the interfacial energy. With time, the two phases of the emulsion will tend to separate, in order to reduce the interfacial area and subsequently the free energy of the systems. Therefore, the emulsions resulting from aqueous dilution are stabilized by conventional emulsifying agents who form a monolayer around the emulsion droplets and hence, reduce the interfacial energy as well as providing a barrier to coalescence[4]. The overall process of the self emulsification is described in the Figure No.1.

Characterization of self emulsifying drug delivery

At initial stage of self-emulsification valuation is visual characterization. The capability of self-emulsification could be estimated by determining the rate of emulsification, droplet-size distribution and turbidity measurements.

Visual Assessment

This parameter gives powerful information about the self emulsifying and micro emulsifying quality of the mixture and about the resulting dispersion[13].

Turbidity Measurement

This parameter is to identify efficient self emulsification by establishing whether the dispersion reaches equilibrium rapidly and in a reproducible time[14].

Droplet Size

It is the major 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 below 50μm leads to the formation of SMEDDSs, which are stable, isotropic and clear o/w dispersions[15].

Zeta Potential Measurement

These factor is 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[16].

Viscosity Measurement

These is the parameter in which viscosity of diluted SEDDS formulation that is microemulsion is generally determined by rheometer such as Brookfield Viscometer.

SOLIDIFICATION TECHNIQUES USED FOR THE CONVERSION OF LIQUID SEDDS TO SOLID SEDDS

Filling of capsules with liquid and semi-solid self emulsification formulations

This is the common and easiest solidification techniques. In these procedure the filling of liquid or semi-solid self emulsifying formulations into hard or soft capsule shells. For liquid self emulsification formulations, a technology technique is used which is called Liquid-Oros technology which used osmotic properties where the layer expands when it comes in contact with water and is pumped into the hard or soft gelatin capsules.

For the semi-solid self emulsifying formulations, the semi-solids are heated to a temperature twenty degrees above their melting point. The molten mixture is placed in the capsule shell with a stirrer. The capsule is capped and left to cool[17].

Spray Drying

By the use of these method in which the preparation of a formulation by mixing lipids, surfactants, drug, solid carriers and solubilization of the mixture before spray drying. The soluble liquid formulation is atomized into a spray of droplets. The droplets are introduced into a drying chamber; the volatile vehicles evaporate leaving behind small particles are collected and used for the formulations of self-emulsifying tablets and capsules[18].

Adsorption to Solid Carriers

The conversion to solid carrier technique is simple technique for preparation of self emulsifying powders. It requires the mixing of liquid self emulsifying formulations and solid carriers in a blender. The resultant can further be used in the formulation of self emulsifying tablets and capsules. Liquiself emulsifying formulations easily stick to the solid carriers. The solid carriers that are used include cross-linked polymers, such as cross-linked sodium carboxyl methyl cellulose, cross-linked povidone, or nano-particles absorbents such as charcoal, bamboo charcoal, porous silicon dioxide[19].

Melt Granulation

It is process in which powder collection is occured through the addition of a binder that melts or softens at relatively low temperatures. The melt granulation gives several advantages compared with conventional wet granulation, since the liquid addition and the subsequent drying phase are omitted. Moreover it is also good alternative to the use of solvent. The melt granulation process was usually used for adsorbing liquid self-emulsifying drug delivery[20].

Melt Extrusion/Extrusion Spheronization

This is a solvent-free technique. These process includes drying of the ingredients, that is, drugs and excipients, addition of a liquid binder to wet the mixture. The mixture pressed with pressure and controlled temperature. The process occurs when the formulation form spheroids of same size. These spheroids are dried and may be coated. The melt extrusion/extrusion spheronization technique is used in the pharmaceutical industry[21].

Spray Cooling

It is also known as spray congealing. In these technique the preparation of molten formulation by mixing lipids, surfactants, and drug. Then it is sprayed into a cooling chamber. The molten droplets congeal and recrystallize into spherical solid particles which collect in the bottom of the chamber as fine powder. The powder may then be used for preparation of solid dosage from such as capsules, tablets etc. To atomize the liquid mixture and to generate droplets, different atomizers can be used but ultrasonic atomizer is most preferred[22].

Supercritical Fluid Based Method

In these technique the lipids in supercritical fluid based methods for coating of drug particles, or for producing solid dispersions. The procedure for occurring solid particles take part in dissolving the drug and lipid-based excipient(s) in an organic solvent such as methanol and then in a supercritical fluid, followed by lowering the temperature and pressure conditions to reduce their solubility in the fluid.

Supercritical fluid based methods is best suited for highly potent, low-dose drugs due to its highest potentials for lipid exposure and a relatively lower drug loading capacity. Commonly used supercritical solvents include carbon dioxide, nitrous oxide, ethylene, propylene[23].

DOSAGE FORMS OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

Self-Emulsifying Capsules

Capsules having conventional liquid self-emulsifying formulation, upon administration form droplets of micro emulsion spontaneously and then disperse in gastro intestinal tract and yield improved absorption. The disadvantage in this self emulsifying capsules which cause decrease in drug absorption is the irreversible phase separation of micro-emulsion which may take place. In cases

where this may occur, the anionic surfactant, sodium dodecyl sulphate is added to the self-emulsifying formulations to improve absorption. A less quantity of polymer is used in the preparation to formulate super-saturable SEDDS to prevent precipitation of drug ensuring a supersaturated state is generated and maintained *in vivo*. These formulations have a decreased amount of surfactant so the side effects relating to the gastrointestinal tract are minimized.

Apart from filling in liquid formulations in capsules, the liquid self emulsifying formulations can also be filled in solid or semi-solid state by combining the liquid with a solid carrier[24].

Dry Emulsions

These dosage form are mainly oil-in-water emulsions which use techniques like spray drying, rotatory evaporation, freeze drying or solid carrier adsorption to get converted into actual powders. They are solid dosage forms. Before use, these powders maybe re-dispersed into water. These formulations are powders that undergo self-emulsification *in vivo* or when they make contact with aqueous solution.

In technique of rotator evaporation, mineral oils and sucrose are used to obtain glass emulsions in the form of dry foams. Surfactants are not required in this technique. Spray-drying technique is mostly used in the formulations of dry emulsions. Also dry emulsions were prepared by spreading liquid self emulsifying formulations on a glass plate and left to dry and further mixed to powders. This dosage form technology inhibits the use of toxic organic solvents and eradicates all the stability problems associated with a typical emulsion like creaming, phase separation, micro-organism contamination during storage. For the oil phase of dry emulsion formulations, medium chain triglycerides are used. Dry emulsions can be used to further the formulation of tablets and capsules[25].

Self Emulsifying Solid Dispersion

Solid dispersions are being used to increase the dissolution rate and bioavailability of poorly water soluble drugs although stability is a major concern during their manufacturing. Hot-melt granulation is a widely used technique for the preparation of solid dispersion. Self emulsifying solid dispersions may be filled in capsules in the molten form[26].

Self Emulsifying Tablets

Preparation of Self Emulsifying Tablets involved adsorption of nanoemulsion on granular materials and then compressed to form tablets. The parameters of dissolution of optimized self-emulsifying tablet showed 80-90% drug release in 45 minutes. The self-emulsifying tablets have been successfully formulated. The aim was to create self-emulsifying tablets that would not require a large amount of solid excipients, and for this, a gelling agent called colloidal silicon dioxide was introduced. The gellies helped to minimize the amount of solid excipients required for the formulations of self-emulsifying tablets and also to cause slow or sustained release of drug, hence the name[27].

Self Emulsifying Sustained-Release Pellets

The self emulsifying pellets have a lot of advantages such as ease of dispersion in gastrointestinal tract, flexible manufacturing environment. Hence, the need to join the good characteristics of pellets with the characteristics of SEDDS led to the formulation of self-emulsifying sustained release pellets. Self emulsifying pellets were prepared using the extrusion/spheronization[28].

Self-Emulsifying Beads

In self emulsifying systems, solid dosage forms can be developed by using less amount of excipient i.e. by formation of Beads. The 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 and humidity. Geometrical features of porous materials like bead size and pore architecture governs the loading efficiency and *in vitro* drug release from SES loaded porous poly styrene beads[29].

Self Emulsifying Nanoparticles

It can be prepared by solvent injection method, sonication emulsion-diffusion-evaporation method. In solvent injection method molten lipid mass containing lipid, surfactant and drug is injected drop wise into a non-solvent system. Larger particles are

removed by filtration and then filtrate is dried to get nanoparticles. Self emulsifying nanoparticles have been formulated by a technique which involves the melting of drug, lipid and surfactants together, the mixture is injected in a stirred solvent drop wise. The resulting nanoparticles were filtered and dried. The technique employed in self emulsifying nanoparticles is known as the solvent injection technique. A second technique is called sonication emulsion-diffusion-evaporation[30].

Self Emulsifying Suppositories

Some studies have shown that solid self-emulsifying drug delivery systems which can increase gastrointestinal absorption also have the properties to increase rectal and vaginal absorption[31].

Self Emulsifying Implants

The self-emulsifying implants have shown elevation in solid self-emulsifying drug delivery systems. Co-polymers that have a hydrophilic region and about 2 functional groups that can be cross-linked are used in the manufacture of self-emulsifying implants. These co-polymers are used as sealants[32].

APPLICATIONS OF SELF EMULSIFYING DRUG DELIVERY SYSTEM

Improve oral bioavailability of poorly water soluble drugs

In the poorly water soluble drugs dissolution rate dependent absorption is a major factor which affects the bioavailability. The ability of SEDDS to release in the drug to GIT and disperses to micro emulsified form. As the globular size is so small subsequent increase in specific surface area enable more efficient drug transport through the intestinal aqueous boundary layer and through the absorptive brush border membrane leading to improved bioavailability[33].

Delivery of Peptides

These technique have ability to deliver macromolecules like peptides, hormones, enzyme substrates and inhibitors by protecting them from enzymatic hydrolysis. These systems are formed spontaneously without aid of energy or heating thus suitable for thermo labile drugs such as peptides. e.g. the intestinal hydrolysis of pro-drug by cholinesterase can be protected if Polysorbate 20 is emulsifier in micro emulsion formulation[34-38].

Figure No.1 Mechanism of emulsion formation after interaction with aqueous media. The primary movement removes the oil from the solid support to form a system, which has low free energy, due to low interfacial tension. After further agitation, the entropy change favouring dispersion is greater than the energy required to increase the surface area of the dispersion and the free energy (ΔG) is negative. The surfactants decrease the interfacial tension, thus reducing the free energy while maintaining the reduced droplet size. In absence of surfactants, the oil droplets coalesce thus reducing the free energy of the system.

Table No.1: Marketed products of self-emulsifying drug delivery system

Product Name	Drug	Strength (mg)	Use	Dosage Form	Composition	Manufactured By
Vesanoid.	Tretinoin	10	Retinoid which treats the leukemia.	Soft Gelatin Capsule.	Beeswax, Butylated hydroxyanisole, Disodium Edetate, Soyabean Oil.	Roche Laboratories Inc.
Accutane.	Isotretinoin	10, 20, 40	For the treatment of acne.	Soft Gelatin Capsule.	Beeswax, Butylated hydroxyanisole, Disodium Edetate, Soyabean Oil, Glycerine.	Roche Laboratories Inc.
Aptivus.	Tipranavir	250	Antiretroviral Agent.	Soft Gelatin Capsule.	PEG 400, Vitamin E, PEG Succinate, Propylene Glycol.	Boehringer Ingelheim Pharmaceuticals, Inc.
Gengraf.	Cyclosporine A	25/100	Immunosuppressive Agent.	Hard Gelatin Capsule.	Alcohol, PEG NF, Polyoxol 35, Castor Oil, Tween 80, Propylene Glycol.	Abbott Pharmaceuticals.
Neoral.	Cyclosporine	25/100	Immunosuppressive Agent.	Soft Gelatin Capsule.	Corn Oil, Mono-di-triglycerides, Polyoxol 40, Castor Oil NF, Tocopherol.	Novartis Pharmaceuticals.
Fortovase.	Saquinavir.	200	Antiretroviral Agent.	Soft Gelatin Capsule.	Medium chain Mono and diglycerides, Povidone, Di alpha Tocopherol, Glycerol.	Roche Laboratories Inc.
Norvir	Ritonavir	100	For the treatment of HIV-1 infection.	Soft Gelatin Capsule.	Ethanol, Butylated Hydroxytoulene, Oleic Acid, Polyoxol 35, and castor oil.	Abbott Pharmaceuticals

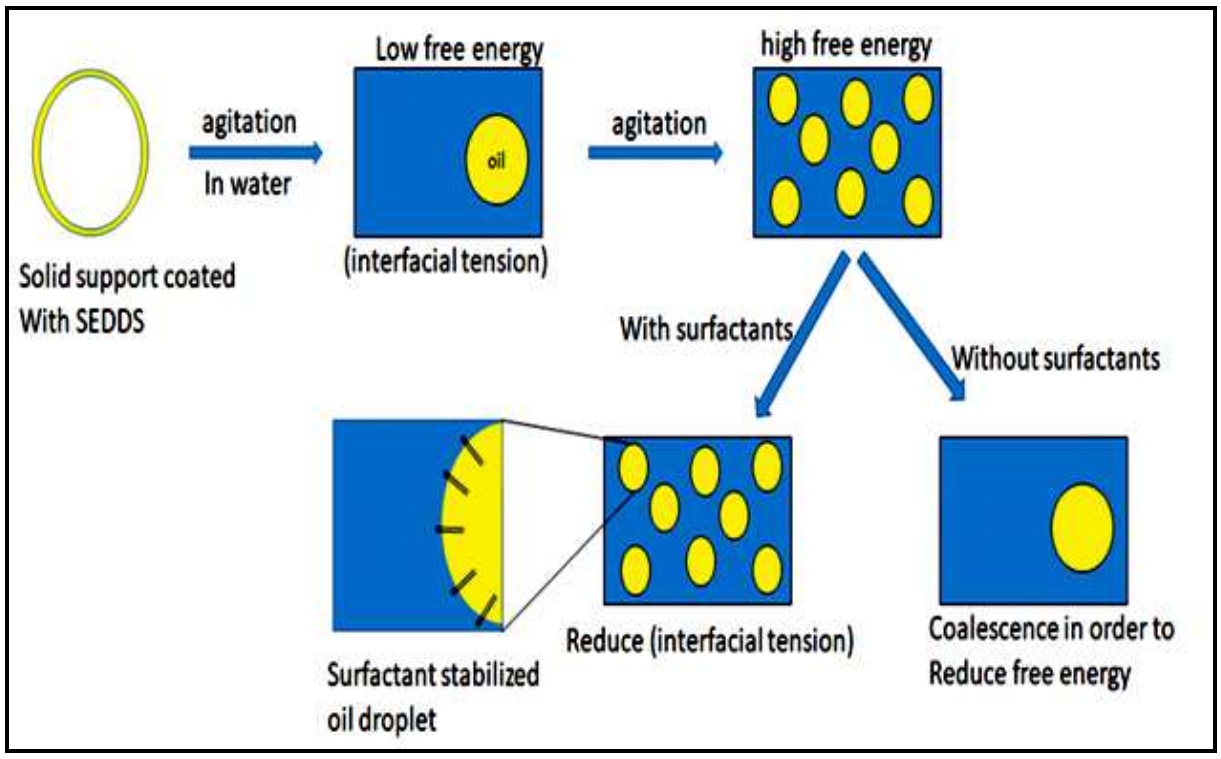

Figure No.1: Mechanism of emulsion formation after interaction with aqueous media

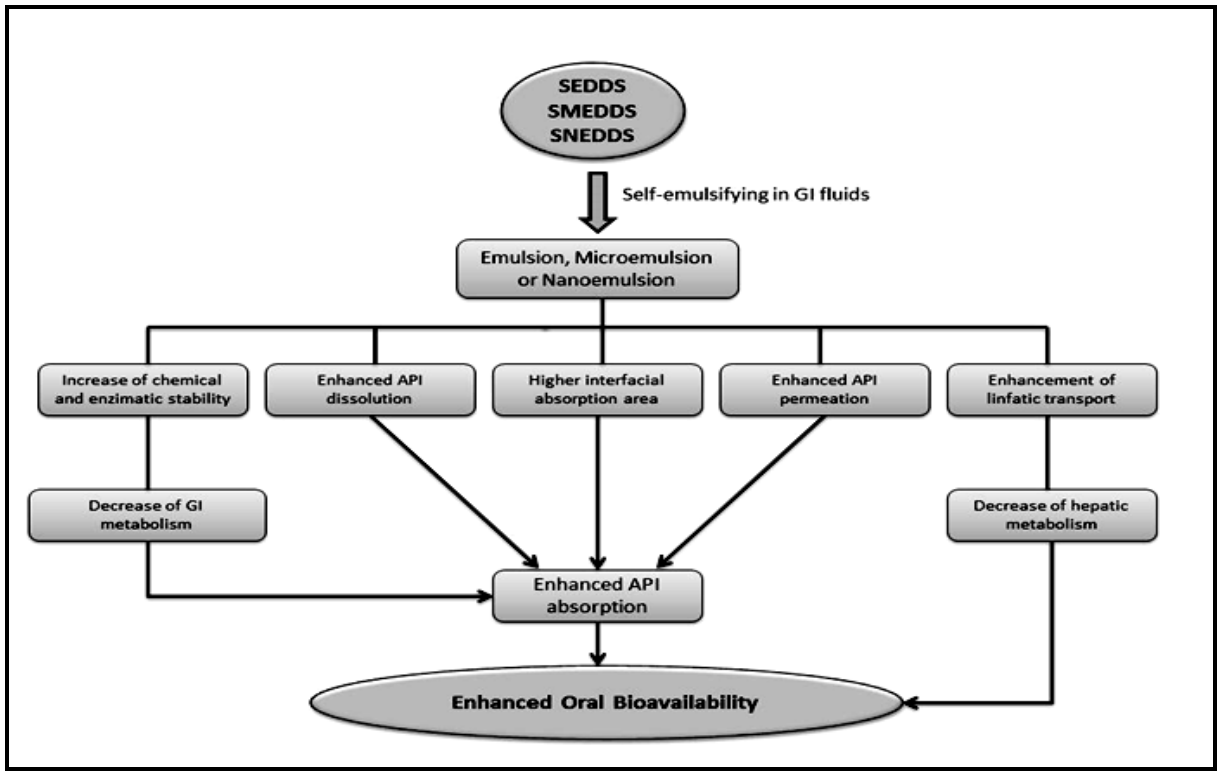

Figure No.2: The factors which are responsible for influence the bioavailability of drugs which are formulated in SEDDS, SMEDDS, SNEDDS

CONCLUSION

This review paper gives details on self-emulsifying drug delivery systems and its main advantage to improve the solubility and bioavailability of poor water-soluble drugs. SEDDS also help in improvement in solubility and absorption of the poorly water soluble drug as well as intestinal permeability. Self-emulsifying drug delivery systems are a promising approach for the formulation of drug compounds with poor aqueous solubility. The oral delivery of poorly water soluble drugs can be made possible by SEDDSs, which have been shown to substantially improve oral bioavailability. In the future formulation of this technology, SEDDSs will continue to enable novel applications in drug delivery and solve problems associated with the delivery of poorly soluble drugs. The preferable solid self emulsifying drug delivery systems to liquid formulations because the disadvantages of liquid self emulsifying formulations are eliminated. SEDDS are used for drugs of BCS class II which have low solubility and high permeability.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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